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WILLIAM ALLEN PUSEY—A LEADER IN ORGANIZED MEDICINE

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An examination of the "Transactions" and other official records of the American Medical Association reveals that from the beginning of the organization, in 1847, until now the names of men distinguished for their scientific attainments, for their devotion to the cause of medicine and for their interest in the public welfare appear frequently.

In the records of early days are found the names of Chapman, Davis, Holmes, Sayre, Sims and many others of equal distinction, leaders who developed plans and defined policies designed to strengthen and perfect medical societies so that they might most worthily achieve the objects for the accomplishment of which such societies were created. As the years have passed official records have become dotted with the names of many leaders of scientific thought eminent as practitioners who in their otherwise busy lives found time to play a full part in the affairs of the professional organizations and rendered unselfish and devoted service in that connection. Among them the name of William Allen Pusey stands out as that of one ever willing and ready to assume a full share of work, however arduous, and of responsibility, however great.

The devoted son of an honored father, whose name is still revered in the community and in the state where he ministered to the sick and steadfastly maintained the highest professional ideals and traditions, Dr. Pusey in the very beginning of his career affiliated himself with the societies in which membership was open to him. From that time to the present his interest in medical organization has never lagged and his willingness to serve his fellows has never diminished. His service in the ranks and later in exalted positions has been marked by a spirit of selfless devotion, by tireless energy and by splendid efficiency in the performance of duty. Those who have been privileged to be associated with Dr. Pusey in organizational affairs have never known him to fail to respond to any call for counsel, for assistance or for work. Many

times he has promptly responded to such calls and has shown himself ready to assume any necessary task without even knowing the nature of the occasion for which his services were sought. It is one of the glories of the American Medical Association, of its constituent state medical associations and of its component county medical societies that the willing and unselfish service of men such as Dr. Pusey has been so readily available.

This is not the place to record in detail the manner and the places in which Dr. Pusey has labored for medicine, for his fellows in their societies and for the public good. In the county society, in the state society, in the national organization and in the societies concerned with the special field of medicine to which his practice has been confined Dr. Pusey has carried a full share of the work to be done. In all of them he has been honored in a manner showing that he had won the confidence, respect and esteem of his fellows, having been exalted by them to the highest positions. In every instance the duties imposed on him have been discharged with fidelity and with efficiency of such quality as to reflect honor on the societies themselves.

WILLIAM ALLEN PUSEY—THE EDITOR

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Up to 1920 the dermatologic profession of the United States was apparently well served by the *Journal of Cutaneous Diseases.* For several years, however, there had been great moans of sorrow and anguish over the special assessments inflicted on members of the American Dermatological Association to support it. There were years in which the individual members of this body had paid from $60 to $100 each in order to secure any kind of medium for scientific expression and the advancement of their specialty. In that year, stimulated no doubt by the success accorded to other special periodicals published by the American Medical Association, Dr. William Allen Pusey suggested to Dr. George H. Simmons, then Editor and General Manager of the American Medical Association, that the American Medical Association take over the *Journal of Cutaneous Diseases* and develop it as a scientific periodical similar to those already available in the fields of internal medicine, diseases of children, and neurology and psychiatry. The amalgamation was promptly accomplished, and the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY was born in 1920. The chief editor selected for the publication was Dr. William Allen Pusey, and until this issue the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY has had no other.

As assistant to Dr. George H. Simmons and subsequently as Editor of the publications of the American Medical Association, it has been my privilege and my pleasure to be rather closely associated with Dr. Pusey in the problems concerning the publication of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. While not world convulsing in their effects or even exceedingly serious as to their solution, these problems have possessed an interest to delight the minds of all who are interested in good medical writing. There have been but few occasions of difference in the views of Dr. Pusey and those of the editorial staff of the American Medical Association in relationship to questions which have arisen. I can remember well the intense and heated discussions concerned with the use of "Treponema pallidum" or "Spirochaeta pallida" and the more recent debates on "dermia" or "derma" as an ending. Dermatologists attach great importance to such matters, in fact even more importance than is given to nomenclature in almost any other branch of medicine except parasi-

tology. It has even been insinuated that dermatology is almost wholly a science of nomenclature. Yet Dr. Pusey's reasoning has always been sound and he has never been averse to searching original sources for authentication.

Dr. Pusey has a forthright method of expression in what he writes closely resembling the diction with which he speaks. Such usage is obviously derived not only from Anglo-Saxon forbears in the Kentucky hills but also from an intelligent and cultured interest in Anglo-Saxon writing which has persisted since his first acquaintanceship with English classical sources. His reading, as I might know, if in no other way, by the books that I have loaned to him, is extremely catholic, in fact, all embracing. It runs the gamut from scientific texts through biography, history and travel to literary criticism, fiction, art and humor, and he is not at all averse to poetry if it has some rhythm and feeling in it even if it does not rime.

The ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY under his editorship has come to occupy a place in the very forefront of dermatologic literature throughout the world. Its status is recognized in scientific circles abroad. Indeed, there is probably no other single dermatologic publication anywhere else in the world so completely meeting the needs of the dermatologist for announcements of research in his field, clinical reports, news, editorial comment, the proceedings of dermatologic societies and abstracts of the significant dermatologic literature. In this development Dr. Pusey has been able through a personal loyalty to himself tendered by many of the younger men in dermatology to obtain the necessary cooperation and assistance for the kind of development that the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY has had. Lest any one feel from this that Dr. Pusey has delegated any of his responsibilities, it can now be said that he has personally passed on every contribution submitted to the ARCHIVES during his incumbency as Editor, that he has personally surveyed all the proceedings of societies and abstracts, that he has personally prepared his editorial comment and that he has repeatedly discussed with the managing editorship in the headquarters office of the American Medical Association every typographic, mechanical, copy-editing or similar problem that has concerned his publication. On many mornings at about the time when civilized men were having their breakfast throughout the Middle West, Dr. Pusey was already sitting in the office of Dr. Simmons or of some of the editorial assistants in the headquarters office awaiting the time when these discussions so near to his heart could begin. And I might as well confess that on many a morning I have come into my room to observe great streaks of the peculiarly adherent and viscid ashes left by the kind of little cigars that Dr. Pusey smokes, the visible evidences of a previous nervous visit by the subject of this essay.

So persistent and inborn is the Pusey interest in problems of writing and editing that his most recent communication to me is concerned with the objection to such words now widely but wrongly used as "intriguing" and "healthful." If the reader should chance to pick up anywhere a piece of writing which is exceedingly direct, in which words like "I have gotten" stand forth bluntly and in which the phraseology is stripped of sham and adornment, he will recognize a scientific contribution by Dr. William Allen Pusey.

WILLIAM ALLEN PUSEY—THE EDUCATOR

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An adequate portrayal of the educational career of a man of eminence must be based on the various ways in which he has expressed himself in life. Dr. Pusey possesses a multiplicity of modes and manners of expression. He is a lucid writer, a good speaker, a clear thinker, an ardent worker and a stimulating teacher, and he has a gift of story telling and a genial personality. All these attributes appear in well balanced relation to the whole man. One might therefore expect that such a combination of qualities and faculties would evolve a character designed "to plow deep furrows and to draw sharp lines."

His biographer will relate that he was born in Elizabethtown, Ky., in 1865, not far from the birthplace of Lincoln. For a generation Kentucky had been the center of the great controversies between the South and the North. One of the oldest universities of the United States, in Transylvania County, N. C., had been established in that region as an expression of the ideals and the vigor of the people. Any one born in Kentucky at that time was likely to come under the influence of the stimulating life and culture which had developed there. Such factors mold and modify men. They furnish a background which enables one to understand and interpret behavior and conduct.

Reaching maturity in such an environment, William Allen Pusey began his educational career early. He was precocious. He obtained the degree of Bachelor of Arts at 20, that of Master of Arts with membership in Phi Beta Kappa at the Vanderbilt University at 21, and that of Doctor of Medicine at the New York University at 23. He began the practice of medicine in 1889, at the age of 24.

After graduating in medicine he prepared himself for his specialty in a characteristically thorough fashion. He took postgraduate instruction in New York. He worked in European clinics for several years at two different times, his course there being interrupted by the death of his father. On his return from Europe he continued for a time the general practice of medicine, taking over that left by his father at Elizabethtown, Ky. Then in 1893, he located permanently in Chicago, where he continues to this day not only to practice his specialty but to engage in a large way in the promotion of almost every activity associated with the progress of medicine.

Soon after his arrival in Chicago he associated himself with the College of Physicians and Surgeons. In the 1893-1894 catalog, his name appears for the first time with the title professor of dermatology; he was scheduled to give a one hour lecture and to conduct clinics each week throughout the year for third year medical students. He continued this educational work for twenty years, winning the unqualified approval of both faculty and students. He became emeritus in 1914.

In 1893-1894 at the College of Physicians and Surgeons there was a notable array of medical leaders. A roster of the faculty at that time reveals, among other medical celebrities, the names of Fenger, Murphy, Steele, Quine, Hektoen, Van Hook, Earle, Evans, Christopher, King, Byford and Holmes. Senn had only recently left the group. Such associates naturally would make a lasting impression on any young man, and no doubt they did on Dr. Pusey, who at that time was only 28 years of age.

Dr. Pusey threw himself with characteristic vigor into the academic work of the institution. After organizing the teaching courses in his special field, he became executive secretary of the college in 1896. As to his rôle as an administrator, I can do no better than to quote a statement by one of his own colleagues, Dr. Charles Davison, who was his loyal friend for forty years. He said:

> Dr. Pusey became Executive Secretary in 1896, and in that year the College began its period of greatest prosperity. The rapid increase in the number of students in the College and consequently its financial prosperity was largely due to Dr. Pusey's vigorous exploitation of the facilities and opportunities the College offered. He succeeded in tripling the number of students in attendance. . . . It was very largely due to Dr. Pusey's ability as Executive Secretary in the early days that there was a College of Physicians and Surgeons with a standing and prestige that the University of Illinois would wish to annex. I would rather have the reputation of the accomplishment of that difficult task than the honor and prestige that being President of the American Medical Association has brought to him.[1]

The first decade of this century was a critical one in the history and development of medical education. Medical colleges were in a bad way. For years standards of admission had been low; much of the teaching was poor, and facilities and equipment were inadequate or entirely lacking. Then a sudden reaction set in. The American Medical Association, through its Council on Medical Education, undertook the much needed reform. One of the first acts of the council was to appoint committees in the various departments to prepare a standard medical curriculum for a four year course. One of the ten sections of medicine established was the Section on Dermatology and Syphilology, and Dr.

1. A tribute to Dr. Pusey at the dinner tendered him by the University of Illinois at the Palmer House, Chicago, March 2, 1933.

Pusey was made chairman of its committee. The work of that committee, after long and arduous deliberations, was completed in a way eminently satisfactory not only to the council but to the profession at large. This report was indeed a landmark in the history of modern medical education. For to this day the latest curriculums in dermatology remain essentially as they were outlined in 1909 by Dr. Pusey's committee of ten.

Again in 1920, Dr. Pusey was called on to serve as chairman of the committee of the Section on Dermatology and Syphilology to prepare a report on graduate training in specialties for the American Medical Association. The aim of the report was to outline a program to prepare applicants adequately for the independent practice of dermatology. This report was made by the committee and published in the *Bulletin of the American Medical Association.*[2] The recommendations were based on a broad view of the requirements in this field, and they served an important purpose in the evolution of the specialty. It is significant to note that from this early report were developed the requirements and general program adopted by the American Board of Dermatology and Syphilology in 1932.

In 1924 Dr. Pusey was elected President of the American Medical Association. He selected for his address before the House of Delegates in Chicago, in June, the topic "The Trend in Medical and Nursing Services." His main thesis was the high cost of medical training. It centered about the important problem of an adequate supply of physicians, especially in the rural districts, and also about the related problem of a more effective distribution of physicians. Dr. Pusey maintained that solutions of these problems might lie along two lines: 1. Improved economic and social conditions in rural districts, including more hospitals and laboratories, better transportation, better roads, more automobiles, ambulance services, etc.—factors furnishing incentives not only for the younger men to enter rural communities but also for the older men to remain in such centers. 2. A change in the preliminary training as follows: Education in an accredited high school as was required at the time, three years of training in a medical college, internship in a hospital of not less than a year and a half, and, lastly, a proper selection of students on the grounds of fitness. According to this plan practitioners were to be turned out in from four to four and one-half years after leaving high school.

Dr. Pusey would not allow that this program in any sense would lower medical standards; he asserted that rather by proper selection of high grade students and more emphasis and time spent on clinical hos-

2. A. M. A. Bull. **15**:29 (Jan.) 1921.

pital and bedside work, the end-product would be more efficient and would be able to render a higher standard of medical service.

One may say, I think, after these twelve or more years, that the first problem has been solved along the very lines suggested by Dr. Pusey. There are now in rural districts and smaller communities improved social conditions, better roads, more automobiles, more telephones, better schools and more and better hospitals and clinics. And few will doubt that more people have better medical and nursing service in the country today than ever before.

As to his second proposal, several of his suggestions have materialized. More emphasis and time are now being placed on clinical and hospital experience. Attention, too, is being directed more and more to the fitness and proper selection of prospective medical students. Witness, for example, the resolution passed by the House of Delegates of the American Medical Association last year, recommending that all medical colleges, in addition to attention to scholarship, give more consideration to character, personality and professional fitness.

The elimination of the college preparatory years, as Dr. Pusey suggested, has not come about. Nor is it likely to come about in the United States, where attendance at the great colleges and universities has become so general, even among the middle and lower classes. In a way attendance at a university today corresponds to attendance at the high school of a generation ago, and it is not now considered a serious difficulty to go to college for two or more years as a general discipline for any purpose whatever.

His latest work in education was done as a member of the Commission on Medical Education, a body composed of nineteen distinguished educators, lay and medical, headed by President Lowell of Harvard University, which, after three years of study, issued its monumental report on medical education in 1932.

Much could be said about the educational activities of Dr. Pusey in relation to his contribution to the science of medicine, to his investigative work, to his published books, to his activities in connection with the National Research Council and especially to his important activities as director of the division of medical science for A Century of Progress during the years 1933 and 1934, which was essentially a great educational enterprise. But these are more or less specialized topics to be treated in a more detailed manner by other contributors.

WILLIAM ALLEN PUSEY—THE HISTORIAN AND LITTERATEUR

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Samuel Johnson once remarked that historical writing was a very inferior kind of literature, merely a monotonous record of facts, requiring no imagination and little invention, and fit only to be compared to poor poetry. Like many of the dogmatic utterances of the famous doctor, like many familiar epigrams and proverbs, the statement was only partially true even for the time when it was made. It is less true today. For now more rigorous demands are made of the historian. He must write something other than a dreary record of dates or descriptions of battles, plottings of royalty or the amours of courts.

The modern historian is of course expected to record facts; this is a fundamental requirement. He must know these facts to be true not because he has read them in the pages of some previous writer but because he has verified them at the source. Unless he is preparing an encyclopedic work there must be a discriminating selection of only those facts that are suited to the purpose for which the book is written. Obviously there should be excluded from the one volume epitome of the history of a century much that might appropriately be included in the several volumes devoted to an intensive study of some short though important period of that century. There must be orderly arrangement with proper subordination of minor events and, if there is to be clarity and not confusion, an avoidance of overexplicitness, which so often defeats its own end. Contrary to Dr. Johnson's opinion, the modern historian must have imagination so that he may retroject himself into the past. Only thus can he envisage the life and spirit of the times under consideration. Only in this way can "the values, the qualities, the significance of a period" be understood. Moreover, he must be a philosopher who can interpret events, pass sound judgment on motives, causes and effects, who will approve or condemn not solely according to modern standards but as well by those of the times in which he has for the moment become a participant. Finally, all this carefully selected material, if it is to be effectively used, must be put together

in such form that it will be read because it is attractive and easily understood. The author must be a literary artist possessing that indefinable something called style.

How does Dr. Pusey viewed as a historian meet these requirements? One may justifiably try to answer this question by an examination of his two major historical works, "The History of Dermatology" (1933) and "The History and Epidemiology of Syphilis" (1933).

Naturally there had to be much intensive reading as a special preparation for these two volumes. But intimate familiarity with the facts had already been acquired from years of study that so well qualified him to write and revise his textbook, to teach effectively, to participate actively in the discussions of medical societies, to contribute richly to the pages of medical journals and for twenty-five years to edit acceptably the ARCHIVES OF DERMATOLOGY. He passes creditably one of the severest tests to which a writer is subjected when he makes wise decisions as to what to omit. He has not cluttered up his pages with disconcerting, uncalled for minutiae. He can, in imagination, transport himself back to the earlier periods of dermatology and syphilis. So his comments on men and their beliefs and doings are just, because founded on the knowledge and standards of those times. The views of Willan may seem crude to the present day specialist who knows of bacteria, endocrine glands and allergy; they may have been advanced, even epoch making, for their day.

Then Dr. Pusey is a good deal of a philosopher. He takes a broad view of things. He sees medicine in its relation to other sciences and to society. He realizes clearly that syphilis and diseases of the skin are related to diseases of other parts of the body, that dermatology is but one, and only one, branch of medicine. If somewhat ardently he speaks of his specialty as the gadfly that has pin-pricked other branches to activity, he does it with a half quizzical smile that lets one know that he is not to be taken too seriously. He does not mean to claim—in fact, he does not claim—that all medical progress is due to dermal stimuli. He is a philosopher, too, in that he interprets. And he has convictions. He is not like so many who think that judicial impartiality implies a pretentious presentation of both sides of a question but with an equally pretentious restraint as to expression of personal opinion or arrival at a conclusion. The philosopher should be open minded of course. But, as G. K. Chesterton said, "the object of opening the mind as of opening the mouth is to shut it again on something solid"—as the expression goes, to make up one's mind. Dr. Pusey generally knows his own mind and frankly states his views. To the oft argued question

of the origin of syphilis he has an answer; he takes sides, admitting the right of others to disagree or to be unconvinced as they read the evidence and the arguments he presents.

In addition to all this Dr. Pusey has an easy and pleasing style. He writes interestingly; his pages are not dull. His words are aptly chosen from a well stocked vocabulary. If at times when he speaks from the opposition benches his language is sharp with witty sarcasm, it is tempered by a mellow humor that, antibody-like, prevents an uncomfortable reaction. His sting—if one may speak metaphorically and dermatologically—seldom raises an urticarial wheal.

So, as it seems to me, Dr. Pusey fulfils the conditions that are imposed on the modern historian. Fortunately also, in the two works just considered, as in others, the desire for ephemeral popularity or for the éclat of being the author of a best seller has not tempted him, as is too often the fashion nowadays, to write a book in which facts are distorted or misinterpreted and the sensational is stressed, with the result that a work appears that is unreliable as history, prejudiced as biography, inartistic as fiction.

There is another characteristic shown in his writings, and that is loyalty and pardonable pride. He is loyal to and proud of medicine, dermatology, his native state, the town of his birth, the city of his adoption, his family and his home. This permeates his writings, so that one senses it even though he writes in lighter vein. It is seen in his incidental writings on his specialty, as in his article on Noah Worcester as a pioneer American internist and dermatologist. His "Wilderness Road to Kentucky" reveals him as an investigator, going over and identifying the old trail. He is inspired by his interest in history but largely by pride in his state and in his family—his guide in his studies was the diary of his grandfather, one of Kentucky's honored pioneers. Dr. Pusey has made other noteworthy contributions to Kentucky history in several papers read before the famous Filson Club of that state. Not to be overlooked is his portrait of the saddle-bag physician in "A Country Doctor of the 1870's and 80's." Filial affection has not led him to indulge in excessive praise. He has sketched true to life this noble type of general practitioner, a type which the profession so justly honors.

I should be guilty of an unpardonable omission if I failed to note that Dr. Pusey, like his father, is true to the best ideals of living and of character. This feature, clearly revealed by his writings, will be considered by some other contributor to this symposium.

Were there space, I should like to refer to other writings; I mention but two. His address in 1927 as president of the Chicago Institute of Medicine on "The Importance of Being Historically Minded" is stimulating and philosophical, with bits of wit and humor that add to its interest. In it he takes up the old subject of the science of medicine versus the art of practice. His sensible discussion of the place and value of research, of bedside practice, of empiricism, of the true meaning of science makes the paper well worth reading more than once.

To my mind one of the best things he has written is his Prosser White oration: "Disease, Gadfly of the Mind" (1934). This reveals such a wide knowledge of medicine and cognate sciences, such mature reflection, such historical mindedness and such careful preparation that it deserves a high mark.

Then Dr. Pusey surprised all his colleagues the other day by breaking into poetry: "Late Return." If all free verse were as smoothly flowing as are these few lines, as easily understood, as full of the softer lights of imagery, as revelatory of the hidden springs of man's purer thoughts and actions, there would be fewer critics who still so strongly favor verse after the Elizabethan or mid-victorian manner.

> Shall I go back and face reality
> And see the wreck it makes of dreams of youth,
> Of fancies woven in my retrospections,
> Or save the fond illusions of my childhood,
> And treasure them to the end?
> Shall I go back?
>
> Yes, I'll go back; I have gone back already.
> Old friends have passed, and scenes have changed:
> The lilac bushes in my mother's garden that foreshowed the glories of the growing spring,
> The woodland where I roamed in childish ventures,
> The lanes I traveled on my boyhood rides,
> The farm my father loved, from whom I learned to love the land,
> The home where I was born and learned life's better pleasures,
> The things I hold in memory that make it dear, now I am old—
> All these have passed.
> And I find only dust and ashes—save memory!
> But memory lives and lights anew the visions I have cherished:
> Old friends and places, the fields and brooks and haunts that made youth bright.
> I see them as they were, not as they are.
> And if old friends are gone, or, if not gone, are changed,
> I find new friends to lend kind ears to my recitals,
> To reconstruct the past and make it live again.
> Yes, I've gone back, and found it good.

A study of Dr. Pusey in his avocational excursions into the fields of history, philosophy and polite literature reveals him as a man of extensive knowledge of many subjects other than medicine, of refined tastes, cultured and scholarly. When in the future reference is made to the American physician as a litterateur the names need not be limited to the older group—Oliver Wendell Holmes, Weir Mitchell, Sir William Osler. Others, some still living, have been, and others will be, admitted to this group. As a candidate for membership in this select body may one not name William Allen Pusey? His qualifications grow as his years increase.

It is surely not out of place to drop the rôle of critic and assuming that of friend express the affectionate wish that there may be many such years, years of serenity, of pleasant reminiscence, of enjoyable, leisurely productivity.

WILLIAM ALLEN PUSEY—THE CITIZEN

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"Does your doctor know anything—I don't mean about medicine but about things in general, is he a man of information and good sense?" once asked an old practitioner. "If he does not know anything but medicine the chance is he does not know that."

These words are taken from "The Golden Age" by Mark Twain and Charles Dudley Warner. They seem to apply in a double sense to Dr. Pusey. He is as conspicuous for information and good sense in his activities as a citizen as he is distinguished in medical circles for sound knowledge and wide service.

There is no better title to the claim of good citizenship than the record of a devoted service to the medical science, and if, in addition to giving conscientious care to patients, a physician in any community concerns himself about the public health and the enactment and enforcement of laws and regulations to guard against the spread of disease, surely his services are those of a public-spirited citizen.

If there could be gathered the entire record of William Allen Pusey in scientific research, in spreading information about medical matters by lectures and written articles, in participating with and organizing groups of influential men to urge the adoption of sound laws and the good administration of them, in bearing his full share in upholding the standards and traditions of the profession and in training the young men who are about to enter the profession, it would be a record which, in itself, would entitle him to the highest praise as a citizen.

The story of his life's activity in all these services will be told in other articles.

William Allen Pusey was born in Kentucky. His great-grandfather came to Kentucky soon after the close of the Revolution and played an important part in the development of the state. His activities in the days of Kentucky's rapid growth were recorded in journals and letters. From these early days the forebears of Dr. Pusey were active participators in the drama of Kentucky's development. William Allen Pusey was an inheritor of the high traditions of this state. He grew to manhood during the trying period of recovery from the Civil War. His interest in the history of Kentucky and his appreciation of the contributions made by Kentuckians to the growth of the nation have made of him a student of history.

His first important work expressing his interest in such subjects was "The Wilderness Road to Kentucky," published in 1921, but he has for

many years frequently lectured and contributed magazine articles on historical matters, particularly on the pioneer history of Kentucky.

Dr. Pusey's life has been distinguished by constant but well directed industry. The heavy burdens which he assumed as an investigator and a practitioner of medicine, as an instructor and as a writer and an editor on medical subjects have not prevented him from indulging in keen interest in all intellectual matters or impaired the geniality of his relations with men in different activities. His interests have been wide, and he has always found time to discharge any obligation that he assumed.

In 1928 he became a member of the board of trustees of A Century of Progress and of its executive committee. He threw himself with great enthusiasm into this work. He was at the same time a member of the executive committee of the National Research Council. It was to this body that those organizing A Century of Progress applied for assistance in outlining the general philosophy of an exposition intended to illustrate the services of science to mankind, and it was through the National Research Council that the services of about four hundred of the leading scientists of the United States were secured in an advisory capacity for the development of exhibits. To no one is A Century of Progress more indebted than to Dr. Pusey for the complete and happy cooperation between it and the National Research Council in this the most important phase of the exposition's activities.

As a member of the executive committee of A Century of Progress he outlined the ideals and laid down the methods for an exhibit of the medical sciences. He was supported in this activity by the full confidence of the medical profession. He secured the services of Dr. Eben J. Carey as director of that exhibit, and in the end he had the great satisfaction of observing that there was no department in the exposition which attracted and held the interest of the public to a greater degree than the exhibits of the medical sciences. His efforts represented a service of inestimable value to A Century of Progress.

Dr. Pusey as the chairman of the medical advisory committee of A Century of Progress was able to establish confidence in the minds of the officials of the various national associations in medicine, surgery, dentistry, pharmacy and veterinary science. He possessed and manifested good judgment in the recommendations he made for the various members of the medical advisory committee. He was able to obtain and keep the cooperation of the various exhibitors.

William Allen Pusey is richly endowed by a rare balance of a sound mind, warm sympathy and a keen sense of humor. He has applied these qualities with untiring industry, and he may now regard with pride the results of his labors and, better yet, enjoy the warm affection and the unstinted admiration of a host of friends.

PUSEY'S CONTRIBUTIONS TO CUTANEOUS MEDICINE AND SYPHILIS

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In 1895 a young Chicago dermatologist, Pusey by name, ventured to express an opinion on "Malignant Growths and Their Treatment by the Antagonistic Principle of Erysipelas." The method was at that time a new and radical procedure, a description of which had been published by Coley shortly before. And ever since that day this same Pusey has continued to express himself with vigor and directness on new and old problems of medicine in general and of dermatology in particular, contributing much of value throughout the years and doing it in an altogether delightful manner. His contributions to dermatology have been noteworthy; his editorial comments have been of sufficient importance to deserve separate consideration, and the numerous nonmedical and historical writings as well as the contributions directed to laymen and giving information of medical or dermatologic nature must not be forgotten.

As one reviews any of these four groups of writings, their practical value appears at once. Facts and the correct deductions therefrom have been Dr. Pusey's watchwords. Whether discussing a detailed point in technic or a complicated medical problem, he has reasoned in an eminently practical manner. I doubt not that his early training and environment in the home of a general practitioner of wide reputation inculcated in him the practical nature of medical problems large and small.

In a survey of his long list of dermatologic contributions, books and articles, a systematic presentation of facts, an orderliness of thought and a directness of expression are noticeable. His writings are characterized by a clearcut exposition of the subject concerned as well as by an almost uncanny common sense and an extremely rational point of view of the matter under consideration. He has pioneered in dermatology; he has reviewed; he has summarized; he has philosophized, as the years have passed, and he has stimulated all his colleagues to further medical thought and progress. Considerations on the new, the unusual and the apparently insignificant as well as comments on the old, the usual and the major problems of medicine and dermatology have flowed from his facile pen.

His major medical interests, as judged by his writings, have been the therapeutic use of roentgen rays and syphilis. Roentgen's discovery was made in 1896, and in 1900, four years later, Pusey presented his first article dealing with the subject, entitled "Lupus Treated with Roentgen Rays." From that date until 1908 numerous other articles appeared on the treatment of various cutaneous diseases by this method —pioneering work in days preceding the use of the Coolidge tube and modern apparatus. In 1903 his book on "Roentgen Rays in Therapeutics and Diagnosis," written in collaboration with Caldwell, became the standard for procedure in dermatologic and in all radiation therapy, and it remained a standard for many years. When it is considered that only seven years had elapsed since this new method had been described, it is indeed a matter of major interest that Dr. Pusey and his co-worker had reviewed the field so thoroughly and "recorded the facts" and especially that they expressed so well the need of caution in the continued use of this new agency. Dr. Pusey spoke of "obtaining a not unsatisfactory grasp of the limitations and possibilties of the method" which was in an "early stage of development." His comments on the effect of roentgen radiation on infections, on acne, on cancer of the skin and in general are indeed noteworthy. His "therapeutic indications" for the use of roentgen treatment are, with few exceptions, today, nearly thirty-five years later, as sound as when they were written. He continued to write on the use of roentgen rays in the treatment of cancer until 1915, and in 1923 he looked back on the "Roentgen Ray Therapy of Twenty Years Ago" with the critical eye of one who had participated in the development of that therapy from its earliest beginnings.

In 1900 he discussed the "Present Treatment of Syphilis," and until 1933, when the much needed and delightful little book on the "History and Epidemiology of Syphilis" appeared, he maintained an active interest in that disease. It is natural that he devoted himself to the larger aspects of the contagion, as in "The Present Situation in Syphilis" and "The Sanitary Attack upon Syphilis," but he also realized full well the need of arousing public interest in syphilis as a means to its control, and his booklets on "Syphilis—a Brief Treatise for the Intelligent Public" and "Syphilis as a Modern Problem" were and still are valuable expositions on the subjects for laymen, and it is probable that some members of the medical profession could at least refresh their minds in these clearcut discussions.

The wide extent of his influence in connection with the problem of venereal disease is suggested by his editorials published in *The Journal of the American Medical Association* in the early days of the United States' participation in the Great War. In these articles he reviewed

the programs adopted for the control of venereal diseases by other nations during the war; later he had the opportunity of using this knowledge in Washington, D. C., in directing the training and placing of personnel for the effective treatment and prevention of syphilis. He was, therefore, an important factor in providing effective diagnosis and treatment of syphilis during that period.

In 1907 he published the first edition of his book "The Principles and Practice of Dermatology," and the work was, as could be expected, eminently practical. Written at a time when much change of a revolutionary nature was taking place in dermatology and syphilis, it was and still is a delightful book to read, covering the subject thoroughly, especially with reference to the details of treatment. His book has passed through four editions and is widely used, particularly for the answers to practical problems arising in dermatologic therapy.

He was also a pioneer in the use of carbon dioxide snow in treatment of nevi and other conditions, and his suggestion regarding less expensive molds did much to make this method available for wider use.

Pusey's writings also show his interest in the field of cancer. A pioneer in the treatment by roentgen rays of cancer, both of the skin and of other organs, he wrote vigorously of that treatment in the early days of radiation therapy.

Numerous case reports bear testimony to his powers of observation and his desire to help others. These reports depict the facts clearly and concisely; they contain his comments emphasizing the salient features of the particular disease or throw light on some obscure point.

His contributions to the laity deserve a word. Whether discussing the "Care of the Normal Skin" or syphilis or "Fifty Years of Progress in Medicine," he has had the faculty of putting into words and phrases understandable by the average man the subject under discussion. He has retained the point of view of the physician but has expressed himself in the ordinary language of the listener.

In recent years he has dealt particularly with the larger problems of medicine, historical facts, ethics, ideals, etc., but he has always done so from the practical point of view. Perhaps it is all a part of his "October Views in Medicine," but in any event his choice of words and methods of expression command the attention of his readers and carry a message born of his wide experience in the world.

From such details as "Fissure of the Lip—Advice for Its Treatment" and "An Easy Method of Marking the Skin" to the "Principles and Policies of the Medical Profession in its Public Relations" there is a far reach, but it well represents the wide range of Pusey's contributions to medicine. Nothing with relation to dermatology and medi-

cine in general has been too insignificant and nothing too broad for him to have concrete and constructive ideas on it and to express those ideas to the world at large with clearness and vigor. Many a situation has thus been clarified by his golden touch. May he live long to observe and enjoy the achievements of his written word and the fulfilment of his visions!

WILLIAM ALLEN PUSEY AT CLOSE RANGE

HERBERT RATTNER, M.D.
Member, Editorial Board, Archives of Dermatology and Syphilology
CHICAGO

> The best doctor is the best artist, and the best medical artist is the master, not the servant of his science.
>
> SIR CLIFFORD ALBUTT

Dr. Pusey has been editor of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY for sixteen years. He has made this publication one of the great journals of medicine. Its high position is widely recognized and is a tribute to his leadership. On Dec. 1, 1936, Dr. Pusey celebrated his seventy-first birthday, attaining an age at which general opinion deems desirable retirement from positions of the sort mentioned; and because Dr. Pusey thought it wholesome to respect this opinion, he prevailed on the Board of Trustees of the American Medical Association to relieve him of the editorship. His resignation calls for something more than a casual notice.

Pusey, like Marcus Aurelius, might well say, "To the gods I am indebted for having good grandfathers, good parents . . . good associates, good kinsmen and friends . . . nearly everything good." Those who know Pusey will recognize in him qualities which he not only inherited but doubtless acquired from his surroundings.

The members of his family were Kentuckians who had come from Virginia and Maryland in the pioneer days of the state; all of them had been in America from early colonial times. On his mother's side Dr. Pusey is a descendant of the Browns, adventurous Kentucky pioneers who migrated from Virginia in 1782. William Brown, his great-grandfather, is a historically important person in Kentucky, not only because he helped to establish the country during its most perilous period but also because his journals accurately described the roads traveled by the early settlers and their struggles to establish the first state in the wilderness. It was as a tribute to the memory of his grandfather that Pusey wrote "The Wilderness Road to Kentucky."

The Puseys were Quakers, and they were among the pioneers who had come to America with William Penn. The oldest house now standing in Pennsylvania is the Pusey house at Chester, Penn., built by Caleb Pusey, a millwright, in 1683, which is now preserved as a

historical relic. Joel Pusey, Dr. Pusey's grandfather, also a millwright, came to Kentucky from Maryland by way of the Ohio River in 1822. He was a man of education, ideals and ambitions, and apparently prosperous, for he erected several large mills in Meade County and settled his family on a farm of several hundred acres. Three of Joel's sons became physicians; the youngest, Robert Burns Pusey, was Dr. Pusey's father.

His ancestors had been landowners, millers, surveyors, merchants, lawyers and doctors. In one line they have been possessed of wealth and have enjoyed corresponding social standing, and some members of considerable ability have attained distinction. Members of another line have shown a more than ordinary intellectual energy and alertness, an inclination to study their experiences, to be greedy for knowledge and to be speculative and philosophic about the present and the future, and have possessed imagination and ingenuity. For the most part they have been industrious, practical, dependable people, never blazing with a great heat, but always able to keep the family fires burning.

With such a heritage William Allen Pusey was born on Dec. 1, 1865, in Elizabethtown, Ky., "in a rural county in the middle South—a land of red clay hills seamed by fertile valleys." His home environment was that of a prosperous family in a pleasant small town, which afforded a happy childhood that left him remembrances clothed with romance and sentiment—the sentiment he expressed so beautifully in his "Late Return":

> . . . memory lives and lights anew the visions I have cherished:
>
> Old friends and places, the fields and brooks and haunts that made youth bright.
>
> I see them as they were, . . .
>
> . . . I've gone back, and found it good.

Pusey still goes back and still finds it good. In fact, after forty years of residence in Chicago, Elizabethtown is still home to him.

In Elizabethtown Dr. Pusey and his brother have established the Brown-Pusey House, which is the community recreational and cultural center. Mrs. Pusey, who was Sallie Warfield Cunningham, also was born in Elizabethtown, and it is to Elizabethtown that Dr. and Mrs. Pusey plan to retire, when he "can get around to it."

Pusey's first training was received in a local private school that his family had helped to establish. At 8 years he went to the public school, and he continued to attend that school until he entered Vanderbilt University in 1881. He was not quite 16 years old when he went to Vanderbilt, and he spent four years there as an undergraduate student and one year as a fellow. The new life at college marked

the first great transition in his life; he was now put entirely on his own responsibility. He took his college work seriously, for his father had early impressed him with the importance of a thorough education, and then, too, the intellectual atmosphere at Vanderbilt encouraged study and hard work. The record he made there portended a brilliant career. He was popular and active in college affairs and held numerous offices. He was given honor certificates for proficiency in Greek, chemistry, natural history and geology and certificates for distinguished proficiency in Latin, physics and astronomy—a good record and unusually interesting in that the subjects were so widely diversified and so far removed from medicine. He was graduated with the degree of Bachelor of Arts in 1885 and was chosen class valedictorian. His paper on "Should the Classics Still Be Studied?" was sophomoric but was a strong address that would have done credit to an older and more seasoned scholar. In it he defended the teaching of the classics because it "refines taste, quickens sensibilities and disciplines reasoning powers." Of course he was but 20 years old at the time, and it is of interest that when some years later he addressed the graduating class of the University of New Mexico, and more recently the alumni of Vanderbilt, he reversed his early stand to approve whole-heartedly the attitude of the modern educators who stress the importance of early training in things more practical along with the study of the humanities.

The year of his fellowship was especially valuable, for in addition to rounding out his college work he devoted much time to medical studies and developed his interest in writing. During this time he was business manager of the school paper and contributed numerous articles to it, usually historical papers or biographic sketches. Undoubtedly the years at college exercised an important influence in his subsequent life; he worked hard but enjoyed it, and he has often said that those years were as happy as any he has had.

In the fall of 1886 Pusey entered the Medical College of New York University, and after his experience at Vanderbilt found it disillusioning. The medical school was the old style proprietary instition, the reason for the existence of which was chiefly the prestige that teaching positions gave to the faculty. The period was an interesting one. Bacteriology had just been introduced to revolutionize the practice of medicine, and even at that time there were some among Pusey's teachers who failed to accept its importance. By the end of his first year he stopped attending most lectures, for he found that he could do better by studying alone. He took private quizzes and at the end of the second year was graduated among the first ten in a class of about two hundred students. His teachers, he

has since remarked, were able men, and for the most part he respected them, but they were hampered by the prevailing system. He left New York University with no gratitude and without having acquired for it the affection that he had for Vanderbilt. In 1891, when he had just left medical school, in an article on "Medical Education—From the Student's Point of View," he forcefully criticized the system of didactic lectures then in vogue and suggested that an effort be made to make of the student an active agent in the exchange of ideas between teachers and students. It is interesting that this, his first medical paper to be published, was in criticism of medical education.

His record at medical school, while good, was in no way remarkable. He was graduated without clinical training. Fortunately he had had a great deal of that with his father. Since he was a young boy Pusey had been riding the countryside with his father on his rounds of visiting patients. As he became older the privileges were extended, and by the time he was in medical school Pusey had an intimate acquaintance with his father's practice. During his school years he and his father carried on a regular exchange of interesting letters, many of which dealt with medical subjects, particularly the newer teaching. Out of this association Pusey gained a clinical experience that stood him in good stead in later years. It was a rich companionship in every respect, and that he is mindful of it is evident from the fact that he dedicated his most important work, his textbook, to his father, "whose memory is an inspiration."

It was Pusey's good fortune that after graduation he was not faced with the imperious necessity of making a living. His father believed firmly in the value of postgraduate work, and this, together with the help of his wife, gave Pusey the opportunity to further his training. Pusey made the most of this opportunity. He spent two years working at the Skin and Cancer Hospital, in New York, under the tutelage of George Elliot, and planned to continue his studies in Europe. He and his bride had been in Europe but a few months when his father died suddenly, and Pusey hurried home to take his place as head of the family. It was a serious responsibility to assume at 24 years of age. There was his father's practice to conduct, an estate to settle and the education of four younger children to be completed—that of his brother and that of the three nephews of his mother. Dr. Brown Pusey, of Chicago, and Dr. Hill Hastings, of Los Angeles, both physicians of distinction, attribute much of their success to the able judgment and guidance of their "older brother." The family was not wealthy although there was enough for the needs, and it took capable management for Pusey to keep things going. After spending a year at home, during which he took over his father's practice, he felt that affairs

were running smoothly enough to allow him to resume his graduate work, and he again went to Europe for study. This time he spent nearly two years in various clinics in Europe, studying for periods under the great teachers in Vienna, Berlin, Paris and London. He never remained long with any of them, but with his enthusiasm and inate ability he derived a great deal from his contacts with these men. Throughout, however, he steered his own course.

At the end of two years in Europe he felt that he was sufficiently prepared to practice dermatology. He had had a well rounded education in college, a satisfactory, if somewhat disillusioning course in medicine, a thorough apprenticeship with his father and sufficient experience in general practice to give him the background that he needed. He had mastered enough of the German and the French language to be able to familiarize himself with the literature of medicine, and with his extensive postgraduate work he felt that his training was adequate.

PRACTICE OF DERMATOLOGY

Nothing in Pusey's life has ever been casual or aimless. Generally he has known what he has wanted, and his life has been devoted to the achievement of these things. He settled in Chicago in 1893, the year of the Columbian Exposition. He had thoroughly canvassed the field and decided, as he later told his brother, that Chicago was an excellent place for a man with good training. So without any medical connections, dependent wholly on the contacts he would make personally, he started the practice of dermatology. The first few years were not easy, and, as was usual with most dermatologists at that time, he also treated venereal diseases, but this he gave up as soon as he could, for he had never liked the work. His income from practice was not sufficient, for his brothers still in college required help. To supplement it he was an examiner for the New York Life Insurance Company. It was lucrative work; before long he became local medical director for the company, and a less ambitious person might have settled complacently to this as a career. But it did not fit in with his pattern of things, and after three years he discontinued that work to devote his full time to dermatology.

The year after he settled in Chicago, Dr. Pusey, then 29 years of age, became professor of dermatology at the College of Physicians and Surgeons in Chicago. This was a school of lesser rank than the Rush Medical College or the Northwestern University Medical School, but the doors of those schools were closed to him. He welcomed the appointment and the opportunity it provided to establish a department and to test his own ideas of medical education. He believed it more valuable to instill principles than to teach students to study for exami-

nations, and he soon became a popular lecturer and an inspiring teacher, for his manner was sincere and attractive and his style easy and natural. He became secretary of the medical college, and in that capacity was largely instrumental in effecting the affiliation between the College of Physicians and Surgeons and the University of Illinois. It was a tedious undertaking that required the utmost tact and executive ability to overcome "the usual hot weather wherever doctors are associated together in teaching positions" (S. Weir Mitchell). The affiliation was finally effected, and Pusey saw the college as a part of the University of Illinois grow into a leading class A institution.

He occupied the chair of dermatology until 1915, when he resigned because of other "demands upon his time." It is questionable whether that was the sole cause. I know him to have the opinion that twenty years is sufficient for any one to occupy such a position, and it is probable that this influenced him in his decision to resign. He was made professor emeritus, and while he is no longer active in the affairs of the University of Illinois, he still has a genuine interest in its welfare.

It is of interest that Pusey did not center all of his activities about the medical school. Most of his important work was done independently of it. His pioneer work with roentgen rays was done outside of school. Carbon dioxide snow was developed in his own office laboratory. His books on roentgen rays, "The Care of the Skin and Hair" and "Syphilis as a Modern Problem" were all based on experience gained outside the school. For his textbook, of course, much of the material was obtained from his teaching, and his position with the medical school must have been an important factor in the formulation of his ideas on medical education. Pusey perhaps more than any one was responsible for the incorporation of dermatology into the medical curriculum. His tangible contributions to dermatology, however, were made independently of his teaching.

Much that is of medical interest can be written about the life of Dr. Pusey. First among his important achievements in medicine is his pioneer work with roentgen therapy—in itself a life work.

Pusey's recognition of the possibilities of roentgen rays and his original experiments well illustrate his superb courage and initiative. His work at that time was generally acknowledged to be among the first scientific efforts on a large scale with roentgen rays in the treatment of cutaneous diseases in this country.

It was late in 1895 that the first information concerning Roentgen's amazing discovery of the x-rays was published. Then followed from Copenhagen the reports of Finsen's work on phototherapy. In 1899, Schiff and Freund in Vienna reported on their work with the thera-

peutic application of roentgen rays, Freund describing his attempt to depilate a hairy nevus. Pusey became interested in the new rays and decided to investigate them. In 1899 he went to Europe, spent but one evening with Freund, who was most generous in describing his technic to him, and was so impressed with the work that he never went to see Finsen. He returned to Chicago with an exact duplicate of Freund's apparatus, and with the help of an electrician he reconstructed it without ever having seen a machine in actual operation. His brilliant accomplishments after that are a matter of record.

From 1900 he reported at intervals on his experiences with roentgen rays in treatment of a large number of disorders of various types and on the effects of their use on normal and abnormal tissues. He presented his results without prejudice and recorded both failures and successes. It was valuable work, which aided in the development of roentgen rays as "the most useful and important single agent in the armamentarium of dermatology" (MacKee).

Although Dr. Pusey was favorably impressed from the beginning with the possibilities of roentgen rays, he never became overenthusiastic at the expense of caution, and his reports were always sober and conservative. He reasoned that there was no ground for regarding roentgen rays a panacea for all diseases of the skin and that "The practical problem which has to be solved in applying X-rays to the treatment of skin diseases is to so manage the rays as to attain effects sufficient for therapeutic purposes, without overstepping the limits of safety."

Pusey's pioneer work with roentgen rays seems more remarkable when one considers the dreadful results that were produced by other, less cautious, users. He did not at the time have the advantage of standard worked-out dosage tables. He had only his own clinical judgment to rely on, and yet he can recall only one case in which he carried roentgen treatment to the point where he regretted it. He was able to say: "Not one of my assistants has ever developed any chronic Roentgen ray changes. As respects burns I have been lucky." It was more than luck, for Pusey never used roentgen rays blindly but always employed them with a rational working hypothesis based on Freund's generalizations on the use of roentgen rays in therapy.

He early observed, and I believe he was the first to call attention to the fact, that persons differ in their tolerance of the rays; he said:

> My experience . . . indicates, contrary to the statements of some observers, that with all the factors that determine the strength of the light the same individuals vary considerably in their reaction to the rays.

He was aware from the start of the danger, and he cautioned that roentgen rays should not be used for the treatment of superfluous

hairs, despite the fact that he was stimulated to investigate the possibilities of roentgen irradiation largely because he wanted to treat a patient with an unsightly hypertrichosis—in that case he obtained an excellent result.

Pusey elaborated "indications" for the use of roentgen rays in therapeutics which have stood until today. Among the many new uses for roentgen therapy that he suggested was the treatment of leukemia, pseudoleukemia, Hodgkin's disease and localized hyperhidrosis. He began to use roentgen rays on Feb. 1, 1900, on a patient with hypertrichosis. Soon after, when treating another patient he saw a severe acne clear up. In May 1900 he treated his first patient with lupus; in January 1901 he treated epithelioma, and about six months later, carcinoma of the breast. To quote Dr. Pusey:

> Dr. T. A. Davis has suggested to me the use of X-ray exposures after removal of carcinomas of the breast as a means of preventing the recurrence of the disease. With the facts before us as to the destructive influence of X-rays upon the carcinomatous tissue, this ingenious suggestion is worthy of trial, not ony after removal of carcinomas of the breast, but also after removal of carcinomas in other superficial locations.

Was this the birth of the "modern" treatment for cancer?

In February 1902 Dr. Pusey presented a paper on "Cases Treated by X-rays" before a meeting of the Chicago Medical Society that was one of the two most dramatic and exciting in the annals of the society, ranking with the one at which John B. Murphy made his first report on the surgical treatment of appendicitis.

The paper was more than a report; it was a clinical demonstration of some forty cases of lupus, carcinoma of the breast, of the head and of the neck, sarcoma, keloid, leukemia and various kinds of granuloma; photographs of the patients before and after treatment with roentgen rays were shown. Except for a few cases of epithelioma the whole list represented cases which had baffled the most skilful men of the profession—cases in which the outlook was considered hopeless. The brilliant presentation was enthusiastically acclaimed and stimulated long, animated discussion. Man after man—men known in medical history, Drs. Zeisler, Fenger, McArthur, E. Willys Andrews and A. J. Ochsner—commended Dr. Pusey's success:

> One of the patients, mentioned by Dr. Pusey was operated on by me. I declared the recurrent disease inoperable. . . . I am surprised, not ot say astonished, by the effects produced on such an inoperable carcinoma (Dr. Christian Fenger).
>
> How impressive is the X-ray treatment in every one of these cases, often incurable inoperable cases, already discarded by surgeons (Dr. E. Willys Andrews).

Dr. Pusey's work has been intensely interesting to me because his results have demonstrated that patients whose conditions would have been hopeless without this treatment can still be saved. . . . Some of the patients whom I referred to him who are apparently well today would undoubtedly have died before this time had they not received this treatment (Dr. A. J. Ochsner).

The discussions carried the meeting far beyond the usual hour for adjournment. The meeting was held in the evening; the news of it spread to the profession at once. When Pusey arrived at his office the second day after the meeting he was astonished to find a long line of patients, many on crutches, others hopelessly riddled with carcinoma, filling his waiting room and the corridor leading to it—a pitiful sight. It was altogether an unforgettable experience.

The natural outcome of all Dr. Pusey's observations and large experience with roentgen rays was his book "The Practical Application of the Roentgen Rays in Therapeutics and Diagnosis," written in collaboration with Eugene W. Caldwell, which appeared in 1903. It received enthusiastic reviews from all over the world. The fact that in one year a second edition was found necessary clearly indicates the deserved success of the book.

This book, like Pusey's previous reports, showed a spirit of conservatism which was remarkable when one remembers the brilliant results he had obtained. It was the most complete report yet published on practical roentgen work in relation to medicine and surgery. It was a valuable book, one not merely to be read but to be used as a guide in connection with actual work with roentgen rays.

Methods by which the best results were achieved were carefully described, and illustrations of actual clinical subjects showed the condition before the use of roentgen rays and at various stages of the treatment and finally the results obtained. This mass of clinical data was definite proof convincing the most skeptical reader.

The book has remained a standard for many years, and recently in "Early American Roentgenania," Edward Skinner referred to it as one of the foundations of American roentgenology. Altogether it was a fitting culmination to work that was epoch making in the pioneer history of roentgen therapy in this country.

Occasionally today Pusey reminisces about the early days of his work with roentgen rays, exciting days when he had four machines operating almost all day. He delights especially in recalling the instance in which he saw a "peculiar" reaction on the chest of a patient, a bright red inflamed area which was unlike anything he had ever before seen or heard of in connection with roentgen rays. Pusey, perplexed, pondered over that observation until a few days later, when he heard from a country physician that the patient's erysipelas had cleared up. Occa-

sionally one of his old patients, perhaps a woman to whom he gave postoperative roentgen irradiation for carcinoma of the breast twenty-five or thirty years ago, comes to him with some minor cosmetic complaint. Such visits are always a source of great satisfaction and obviously thrill him no end.

Pusey feels definitely that his results with roentgen rays were much better in the early days than they are today; he said recently:

> We are falling down with our X-ray technique. We are using rays that are too hard and we do not give enough. We had much less trouble in the old days with soft rays pushed to the point where there was a red reaction. We rarely had to curette an epithelioma. At that time I gave repeated exposures at short intervals and never felt happy with a tube until it was pretty well blackened up and pretty hard. Of course the new technique is in convenience and accuracy and ease of application incomparably better than the old technique. There is still, however, the same use for judgments in the quality and quantity of the exposures that is an essential of all techniques.

Pusey still adheres to some of his early practices. When he examines a lesion that has been irradiated he is concerned most with the visible effects present and the interval since the last treatment. He still is guided by clinical judgment.

Pusey's pioneer work in the field of roentgen therapy, aside from being of fundamental importance, was the most important—perhaps the decisive—factor in establishing him as a national figure in medicine.

It was at this time, in 1905, that Pusey suggested the use of solid carbon dioxide, carbon dioxide snow, for the treatment of certain lesions of the skin. Liquid air had been used before for freezing lesions, but it had proved unpractical. Carbon dioxide snow was readily available and inexpensive, produced speedy results and, above all, was useful. He had worked with it for more than a year before he published his results; he designed metal molds and described in detail the technic of application and the mode of operation of carbon dioxide snow. Today it is found in the equipment of every dermatologist, and it is used just as Pusey recommended that it should be used more than thirty years ago; there has been no material change in method, indications or equipment.

During this period Pusey was attending dermatologist at the Cook County Hospital. He became a member of the staff in about 1895 and remained a member for fifteen of the next twenty years, an experience which he regards as his most valuable in clinical dermatology outside of his office. Then, too, besides conducting a large private practice he actively managed a busy dispensary in connection with the medical school. To a man with his absorbing interest in medicine, his extensive knowledge of its literature and his tireless energy, the

wealth of clinical material at his disposal was a mandate to write a textbook. Writing it was a laborious task to which he gave three or four years. Evenings extending late into the night were spent in the basement of his home, where he had set up an apparatus for making photomicrographs. He himself took nearly all the clinical photographs that were used to illustrate the book, and he personally reviewed all the pertinent literature. The book, "The Principles and Practice of Dermatology," appeared in 1907 and has since gone through four editions. It was generously received at the time, as it is even today, and although it was last revised in 1924, it is considered a standard and indispensable work. The book throughout bears the stamp of Pusey's personality; it is not a compilation of abstracts. It was strong, well balanced, practical and full for the time. From a literary standpoint Pusey's lucid and readable style set the book apart from the usual medical texts.

The book was in many respects daring in its conception. More space than usual was given to the principles of dermatology—the anatomy and physiology of the skin and the general etiology, pathology, symptomatology and treatment of diseases of the skin — because ". . . it is highly desirable in any study to be as fully acquainted as possible with the fundamental knowledge of the subject." The discussion on the nature of eczema was regarded by many as heresy. Much dermatologic subject matter was and still is debatable ground—it was in dealing with such matter that Pusey's ability for forceful and clear expression found its best application. "The distinction between eczema and dermatitis is almost as essential as that between natural and artificial ice," he said. He did not hesitate to take a firm stand. The view that eczema could not be distinguished from dermatitis was not original with Pusey, but his forceful exposition of the view in a textbook was without precedent.

Of especial merit and new in a work of that type were the introductory paragraphs to each subject. In these paragraphs one can see Pusey's wide perspective, his large conception of dermatology as cutaneous medicine. They show his unusual faculty for proper interpretation of dermatologic phenomena. These alone would have set the book apart from others. From every standpoint the book is a literary treatise possessing distinctive characteristics that can be read with profit by any physician and with interest by any intelligent person. The frequent requests that come from physicians everywhere for Pusey to revise it again are eloquent testimony of its worth. It is the fate of medical books to age quickly, but there are exceptions. Pusey's "Principles and Practice of Dermatology" has proved to be an exception.

OFFICIAL POSITIONS

Pusey's medical reputation was established early. The official leaders were immediately aware of him as a personality, for aside from his accomplishments in roentgenology and dermatology he had shown his capabilities and courage in medical affairs, and above all he represented the aspirations and ideals of cultured and high-minded physicians. Two addresses that he gave in 1895 attracted particular attention. One, "The Social Position of the Medical Profession," was written but four years after he had left medical school, and, of course, before he himself had attained any particular social position. It seems that the tendency of many physicians at the time was to regard their social position with melancholy. Pusey, on the contrary, was finding life in Chicago good, and in a light, humorous after-dinner address he routed their fears with a recital of fact after fact, referring to physicians who had great influence in public affairs, to others who were the companions of kings, to some who had accumulated fortunes and to others who had married heiresses, adding, "rich women are not careless of social position," and ". . . it is not evident that he [the physician] ever had to sit at the lower end of the table."

It was a perfect after-dinner speech and was later reproduced as an editorial in *The Journal of the American Medical Association.* It might well be reprinted today.

On the same day Pusey addressed a graduating class of medical students on "The Capacity of Medicine." It had been charged in some quarters that medicine was unscientific and that it had not kept abreast with the advancement of other arts and sciences. Pusey undertook to appraise the facts. He reviewed the accomplishments in medicine step by step, comparing them with advances in other sciences, and in no uncertain manner he annihilated the position of the skeptics.

> It would seem that the branch of knowledge that has discovered the essential causes of tuberculosis and leprosy and cholera, that has given to the world such men as Helmholtz, Virchow and Koch and Lister and Joseph Leidy; it would seem that this branch of knowledge needs no defense against the charge of being unscientific. It would seem too that this same science that began the century with a discovery that has practically banished smallpox from civilized communities, and is ending the century with discoveries that promise to give us control of some of the worst scourges that afflict mankind; that has given the world immunity from pain under surgical operations, and has produced antiseptic and conservative surgery; that has banished from us scurvy and yellow fever; and that, on a basis of accurate physiology and pathology, furnishes a rational treatment of disease—it would seem that such a science would not more need a defense against the charge of being impracticable and barren of useful results . . . medicine is not the poor relation of any scientific family.

Largely because of these two addresses the doors to official positions were opened to him. He was given tasks to do, investigative work,

books to review, editorials to write—the kind of work in which he delighted—and he gave to those tasks unbounded enthusiasm. He was ever watchful to resist the machinations of those who were irregular. Several incidents occurred which clearly showed his courage. In 1911 an established medical firm of reputation introduced a "radioactive" remedy, which, it was stated, in the hands of "eminent dermatologists has proved a remarkably efficient and safe remedy for epithelioma, lupus, moles, . . ." The formula was not accurate. The implication was that the therapeutic efficacy of the preparation described was due to a radioactive substance. Pusey carefully investigated the preparation and showed that the mysterious new remedy was in fact a drastic escharotic containing sulfuric acid. He severely criticized the "honored

Fig. 1.—Members of the American Dermatological Association, 1922.

house" for blighting its reputation by embarking on a career of exploitation by introducing proprietary remedies of questionable value. It was a serious charge to make against a firm with influence and high repute. The firm tried for a time to justify its act but finally had to admit an "error in judgment" and soon discontinued the manufacture of the preparation. Pusey, to judge by the numerous letters that he received from physicians throughout the country, by this exposé had done the profession a great service. He personally had much to lose by it and nothing to gain except the satisfaction of a good job done thoroughly. He later received a letter from a son of the founder of the firm (the family was no longer connected with it) that is a treasure —a letter expressing heartfelt gratitude for his "working unceasingly and praiseworthily against deceit of all kinds."

Once, some years before that, Pusey had similarly exposed a company using the name of a large sanatorium for dishonest advertising practices, and on another occasion he had forcefully taken issue with a famous inventor who had some queer unfounded views about roentgen rays. Impeding barriers, no matter how mighty, were unhesitatingly torn down. Is it any surprise that medical leaders were cognizant of him?

It was this same spirit which impelled him to cooperate with firms which he thought were trying to deal honestly with the public in matters of health. One of these efforts a few years ago caused him to be much criticized. At the time dealers in toilet preparations were undertaking to advertise their products through testimonials from movie actresses and socially prominent persons. It was merciless exploitation. Proctor and Gamble asked Dr. Pusey for advice as to how to advertise honestly to the public a new soap, Camay, which they were introducing. "They wanted," he said, "to give the public authoritative advice about the use of soap and water. They suggested that I get a group of dermatologists of my selection to examine the soap and prepare instructions for bathing and the use of soap, and, if they found this soap was of high quality, to certify to that effect." In Pusey's opinion it was a step in the right direction, viz., honestly to educate the public in contrast to exploiting it by exaggeration and misinformation. Pusey undertook the task. When the work was finished he found it was "impossible to authenticate these findings to the public without having some one to certify to the accuracy of the investigation and the statements," and he allowed the firm to use his name for this purpose. I criticized him for this. His reply was that Proctor and Gamble were proposing to do what the medical profession always is criticizing commercial concerns for not doing, namely, coming to physicians for information on medical matters. Could the profession hope to have any influence with business concerns if it was always eager to criticize bad commercial practices but never willing to support good ones? Pusey himself had gone out of his way to condemn severely dishonest commercial practices. Now a firm came to him for help in an honorable course of dealing with the public. Would it be consistent to refuse that help? If he did refuse it he felt he could not escape the charge of his own conscience that his whole attitude was insincere. "I would feel myself a coward, and I don't want to feel that way about myself. I won't do it," he said.

At the time of the Panama-Pacific Exposition, in 1915, the American Medical Association held a congress in San Francisco to commemorate the building of the Panama Canal. A program was arranged to "add another tribute to the memory of those workers of the health

service who made the building of the canal and the significance of the Panama Exposition possible." It was a popular program to which the public was invited, and the subjects selected for consideration had to do with preventive medicine, infections, sanitation and cancer—topics all pertinent to the occasion. The contributors were Vaughan, Pusey, Flexner, Gorgas, Jordan, W. J. Mayo, F. L. Hoffman and Bass. Pusey was asked to present the subject of syphilis. "Syphilis as a Modern Problem" was written for that meeting. Pusey had already gained recognition as an outstanding syphilologist. The period was one of the most interesting in the history of syphilis. Animals had just been successfully inoculated with syphilis for the first time. The organism of syphilis had been discovered. At almost the same time the Wassermann test was announced, and finally, in 1909, Ehrlich introduced arsphenamine ("salvarsan") for the treatment of syphilis. One important discovery following another with such extraordinary rapidity was without parallel in the history of any other disease. There was utter confusion; clinical acumen gave way to the Wassermann test, and arsenic was injected into persons without discrimination. Pusey was one of the few who had sensed the dangers, and several times he had called attention to the fallacy of such practices, saying "The Wassermann reaction is done by human hands and human hands are fallible." He had seen several mistakes, some of them producing wretched consequences, that were made in the interpretation of the reactions. He had written several important articles dealing with various phases of syphilis. One in particular, "The Present Situation in Syphilis," written in 1913, occasioned a great deal of discussion, much of which was severe criticism from high sources, because his views were contrary to those generally held. His position essentially was as follows:

> Our present knowledge gives us no right to believe that salvarsan will lessen the occurrence of parasyphilitic nervous infections—there is some ground for fear that it may predispose to them except in those cases in which it cures the disease . . . if employed vigorously before the disease is generalized there is strong ground for believing syphilis can be aborted.

In substance salvarsan was not the *therapia sterilisans magna* that Ehrlich claimed it to be. One must not be too much afraid of the remedy, but one must not be too bold with it. Pusey had expressed himself freely and clearly on various phases of syphilis. He had definite opinions on the question of venereal disease, the sanitary attack and the social side as well as the medical aspects.

Pusey knew the problems that were confronting physicians and those that should have the intelligent attention of laymen, and he was particularly fitted to present the subject. The monograph "Syphilis as a Modern Problem" was undoubtedly the best exposition of the subject

that had been made up to that time; it was scientific and still plain; it stated facts forcibly and entirely without sensationalism. Pusey considered syphilis from the standpoint of its effect on society, not primarily as a disease which medicine is called on to treat. Probably no other paper on syphilis had as wide an influence on the intelligent layman. He made it clear that syphilis is a public danger and that "its control must come by treating it as a sanitary problem." He did not consider the disease from the point of view of social and moral measures, but he did urge that syphilis should be treated as are other diseases which attain such proportions as to be dangerous to the public. The monograph was altogether a dignified, sane and timely presentation that gave Pusey the authoritative position in syphilology and public health matters that his textbook had given him in dermatology.

It was not surprising, then, that when two years later the United States became involved in the Great War, Pusey was invited by the Surgeon General of the United States Army to become his advisor in matters pertaining to venereal diseases. His task was outlined as follows: "The duties will relate to venereal matters, the standards of diagnosis, treatment, and methods of prophylaxis, and also the supervision and control of the many agencies for the suppression of prostitution. There are to be no rigid limits to your activities." And surprisingly there were none. Pusey, who held the rank of major in the Medical Reserve Corps, had an absolutely free hand, answering only to the Surgeon General. He poured his energy into the work and outlined a program for the handling of the venereal problem covering medical and social problems under which all the work in this field was correlated. At his suggestion the work was put in charge of a committee of five members, the other four members being nominated by him, and he was made the chairman. It was a big job with great responsibility, and he was equal to it. The record of the American forces in this country as to venereal diseases was not surpassed, and it was a tribute to the medical corps. An extremely valuable work was "The Manual of Treatment of the Venereal Diseases," written by the committee. It was regarded so highly that about 125,000 copies of it were distributed by state boards of health all over the country. It was the most comprehensive plan of its kind, and it still serves as a standard for similar projects.

Pusey divided his time between Chicago and Washington, D. C. His task involved colossal labor that only unusual industry and capacity could undertake. He was, in spite of the difficulties, actively directing his associates in the management of his practice. He was serving as consultant dermatologist to several hospitals. Despite the exhausting demands of the work in Washington, D. C., he continued his medical

writings and addresses. His services were constantly demanded by various medical boards and social agencies. His was a full and active life, a road that mediocrity could not have traveled, and he had reached the point where certain demands on him, no matter how exacting, had to be met. It was that sort of a demand that led to his election as president of the Chicago Medical Society.

The incident of Pusey's election and the circumstances that led up to it are of especial importance because they mark the beginning of a new interest for him—the executive side of medicine. For several years the society had been divided into two inharmonious nonreconcilable factions: the "highbrows" and the "lowbrows." Tempers were strained and at each election of officers threatened eruption. The more equable members decided to take decisive action.

Pusey was urged to accept the nomination, for his medical reputation together with his personality made him the perfect "compromise candidate," one highly acceptable to both factions. He was reluctant to accept, but the matter was laid before him in a way that made it impossible for him to decline without seeming to be unwilling to do his part.

Pusey became an active president—not a figurehead—for his executive ability fitted him for the office, and his charm made him popular. With his election there was born a new interest in the affairs of the Chicago Medical Society, and there was a genuine reconciliation between the various factions, which has endured.

He gave to the position much of his time and energy, and his real concern over the problems of medicine and its practitioners made for him innumerable genuine and lasting friendships, which played no small part in his being elected later to the presidency of the American Medical Association.

In 1923, at the Seventy-Fourth Annual Session of the American Medical Association, held in San Francisco, Pusey was made President-Elect of the American Medical Association. This was the first and has been the only time a dermatologist was chosen. He was deeply moved by the honor, for his whole life had been steeped in the traditions of the organization. Another member of his family, a cousin of his mother, Dr. John T. Hodgen, of St. Louis, a famous surgeon of his day, had also been president of the American Medical Association. In the eleven years before, as treasurer of the American Medical Association, Dr. Pusey had been in touch with the intimate workings of the Association; he had learned to know and respect the ideals and "traditions of its leaders and the honest striving of the rank and file." His was a positive personality, and he had often braved unpopularity to carry his point when he felt that the cause was worthy. The elec-

tion meant to him, therefore, an expression of confidence and approval that warmed his heart, that made him proud with "the sort of pride that goes with humility."

It has been said that the qualities that go to make the good physician are intelligence, character and industry tempered by an admixture of that human quality called common sense. Pusey had already proved himself in all respects a good physician, and these same qualities made of him an outstanding leader of medicine. Occasionally a man in a profession expresses a thought so definite, so complete and so concisely stated that it reaches beyond the boundaries of the profession for which it was intended and obtrudes into the consciousness of the laity. That is what happened with Pusey's presidential addresses. His address to the House of Delegates dealt with "The Trend in Medical and Nursing Services." He said:

> The trained nurse for ordinary service has become inaccessible except to the rich and for institutional and community employment . . . The average family cannot pay the salary that the high school graduate who has had three years training in nursing may justly ask.

He recognized the value of high standards in nursing and had no desire to break down what had been accomplished, but the gap between the nurse and the sick person had to be made narrower. This could be done, he felt, by curtailing the high requirements and shortening the course in training schools, for much was being taught which had no distinct bearing on nursing.

On his first meeting with the House of Delegates it was necessary to take issue with them, and he did not hesitate to do so. His comments on medical service were likewise against the current. There was at the time a shortage of physicians in rural districts, and the House of Delegates suggested that districts in need should guarantee a specific income to the physician in order to get him to settle in its midst. Pusey disagreed with this plan, for he reasoned that but one step more would be to hire the physician for all his services, which would ultimately lead to the undesirable panel system prevailing in Europe, and he suggested instead that a solution could be found by means of a change in the system of medical education.

> . . . instead of unconsciously assuming that our present standards of medical education are sacrosanct and suggesting that everything else be changed instead of it, would it be contrary to public policy to have the universal degree in medicine, one which would represent an adequate training for practitioners of medicine, but which would not be exacting beyond all other professions in time?

He suggested a concrete program, namely, after high school education, three years of medical training followed by internship in a hospital of not less than a year and a half, and he recommended careful selection

of students on the ground of fitness. "The requirements of medical schools are to be exacting, and as far as possible integral parts of strong educational institutions. The plan is adequate, sound pedagogically and in line with other technical educations." The essentials of the plan were (1) that the collegiate part of the course should be educationally sound, and (2) that it should include a clinical training through apprenticeship in a hospital, for

> . . . the most essential thing in training for the practice of medicine is a clinical apprenticeship. . . . It [the plan] would leave an opening for that great number of useful men who desire to take up the work of the everyday practice of medicine . . . would not interfere with a few schools whose aim is only to supply the Ph.D.'s of medicine, but the requirements of these schools should be so exacting that their graduates in number and culture would correspond to the Ph.D.'s of the best universities. Fitness, and not a competency in early life, would be the essential requirement for a medical career.
>
> . . . It has been argued for the increase in the medical course on the ground of the vast increase of medical knowldege. Medical knowledge is not static. It is entirely possible that it will increase as much in the next twenty-five years as it did in the last twenty-five years. When that time comes are we going to add two or three or four years more to the preliminary training? Our students are now overloaded with detail . . . one great reason why nearly every student comes out feeling that he must confine himself to one small part of medicine.

Pusey did not underestimate the value of college training, but he valued it for the background of culture that it gives one in his general outlook on life rather than as a necessity for the practice of medicine. He thought that the relatively greater cost in time and money necessary for a medical education puts medicine at a disadvantage with other professions in the eyes of young men, for few young men have an irresistible call for any vocation. The social need of medicine was for more doctors in districts where there was a shortage of them.

These views were not entirely original with Pusey—they represented rather a school of thought. The position that he took was generally dismissed by educators then holding the reins as unenlightened reasoning of a past generation. Coming from a man holding a high office they carried a new meaning. It took intellectual courage to assert his position, and it does not matter that his labors were to no avail. Pusey, of course, in his consideration of medical service to rural districts made one mistake which he has since recognized. He failed to recognize the importance of good roads and of the automobile. But he has not had to revise any part of his views on medical education. He has had widespread support in them, perhaps because, as one prominent educator of the opposing school remarked, "They are dangerous because they are so practical." There is the satisfaction too that those who do see eye to eye with Pusey are without question outstanding practicing physicians,

not theorists, and although his crusade failed in its main objective it did serve to bring the whole question into the open.

In his inaugural message, "Some of the Social Problems of Medicine," an exceedingly important message for which he received wide acclaim, Pusey pointed out that the social organization was undergoing a revolution and that medicine was also undergoing a change. Problems were confronting medicine which needed to be considered with deliberation, imagination and wisdom.

> This government of ours was organized in a spirit of individualism. Given equal opportunity men were expected to work out their own lives through industry, intelligence, and character. Competition was allowed to exercise its wholesome influence in stimulating men in their worldly efforts. . . . Now we have a new dispensation. The trend has been continuously from individualism to socialism. . . . this tendency is certainly humane; whether it is best for the future of man is another question . . . to be determined by the future experience of the present cycle of civilization.

This was written in 1924.

> Medicine is particularly exposed to the dangers of socialization, because the projects of socialism that obtain the first acceptance are those that have to do with health and physical welfare. There is an evident tendency to . . . take it [treatment of the sick] away from the individual's responsibilities and to transfer it to the state; to turn it over to organized movements. If this movement should prevail to its logical limits, medicine would cease to be a liberal profession and would degenerate into a guild of dependent employees.

Pusey urged that medicine join with the enlightened minority that is the salvation of democratic government to oppose the socialistic tendencies, "regardless of their temporarily seductive character," to oppose the various governmental projects for practicing medicine, and the efforts of organizations, public and private, including medical schools and hospitals, to go into the practice of medicine as a business, activities that are "fundamentally wrong; that are throwing to the winds the sound traditions of medicine that have developed from long experience and that from experience have been found to be essential to medicine's character and progress."

Medicine, Pusey thought, should also take a definite position in two other problems which are related to the socialistic tendency—problems which he discussed for the first time officially, namely, limitation of population by birth control and improvement of the race by breeding.

> Those people inherit the earth who multiply most rapidly; and unfortunately fecundity tends to increase inversely according to the social scale. Society will, and should, make every effort to do its best for its weaker members, but there is no good reason why it should not try to stem the tendency to the peopling of the earth by the defective, the unfit and the incompetent.
>
> . . . the subject is of vast importance to the welfare of man; it is one which should have scientific guidance; for this medicine must be looked to, and medicine

should undertake to approach its responsibilities by beginning to give the subject the continuous and serious thought that it justifies.

Such fearless espousal of the principle of birth control by an official of the American Medical Association was sensational. It was without precedent, and in the ultimate history of the idea the inclusion of it in a presidential address will always rank high. Equally timely was his stand on eugenics.

Eugenists were concerned chiefly with an effort to eliminate hereditary disease.

> The real problems of eugenics are those of breeding to improve the physical and mental and moral qualities of the race. . . . No practical man believes that scientific breeding can ever be applied to man as it can be to animals. . . . The only practical step at present is the negative one of taking measures to prevent the increase of those who are socially hopeless defectives. . . . If there is to be effective leadership in this field, medicine must take part in it.

Another of the social problems of medicine that needed emphasis, according to Pusey, was the problem of education of the public in medicine and in regard to medical frauds and fanaticism; for the "audience is for the most part receptive." The greatest problem of all, however, "is the old homely one of treating men that are sick . . . man is still a machine that will get out of order, will be injured and will ultimately wear out. As long as that is true, there will be need for the personal physician to take care of the individual patient. . . . To foster the competence of these men is the greatest social responsibility of medicine."

Probably no other presidential address had given to a convention so much food for thought. It was one of the most important comprehensive and far-sighted statements ever to be placed before the medical profession. The American Medical Association heretofore had been confronted with problems of effective organization. These had been solved. The better minds in the profession had been devoted almost exclusively to the scientific problems of medicine. In the solution of these too they had made tremendous strides. The social problems were real ones too, but the best minds had not yet interested themselves in them.

Pusey pointed the way and urged the medical profession to follow the "sounder, harder course of working for the ultimately best measures of society." His message was a challenge. It was timely, logical and influential, and certainly to judge by the response expressed in newspaper editorials throughout the country, "the audience was responsive."

Pusey suddenly became a public figure. The demands on him were enormous. Numerous invitations to address medical and lay audiences came from all over the country, and he felt obliged to accept as many of these as possible, to foster interest in the problems that were con-

fronting medicine. Medical education and medical economics were topics to which he gave particular emphasis because he thought that their interest extended far beyond the profession alone and that their control was only partly in the hands of medical men. He injected his personality into his official career; he was an aggressive president, and he rendered a splendid service to the profession as well as to the public, who came to realize that the labors of the profession were directed to their interest. "The Association has had no more faithful, no more intensely earnest, active and efficient officer than he. His personality, his industry, his high ideals, his courage, his aggressiveness, his energy, his willingness to serve, his scientific knowledge, and his determination to be useful to the American Medical Association have all contributed to the marking of his official career as one productive to the Associa-

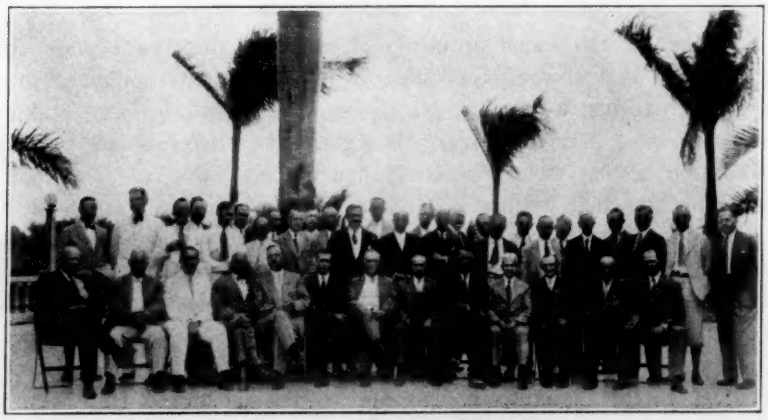


Fig. 2.—Members of the American Dermatological Association, 1932.

tion itself and to all of its membership." (Olin West, Secretary and General Manager of the American Medical Association.)

It is characteristic of Pusey that his service to the Association did not end with the close of his presidency. Even today, as one of its elder statesmen, he gives of his counsel frequently. Only recently, when it became necessary for the profession to state its principles and policies in its public relationship, the Association turned to him. His famous "twelve points" compelled the attention of all students:

PRINCIPLES

1. Medicine is the trustee of society in the care of the sick and injured; its policies must always be governed by this fundamental fact.

2. The good of society must be the sole aim of its public policies and the good of the patient the first consideration in the relations between physicians and patients.

3. Medicine's first responsibility must be to see that its services are available to all men.

4. The public interest demands the most competent medical profession possible. Medicine must be an attractive profession to compete successfully with other professions for the ablest young men.

5. In the sense that every calling from which a living must be gained is a business, medicine is a business; it must accept the competitive conditions of practical life but, as a profession of high ideals, it must seek to prevent selfish commercialism.

6. Experience has shown that the vast majority of disease conditions afflicting man can be most satisfactorily and economically cared for by a competent individual general practitioner.

RESPONSIBILITIES

7. The services of medicine include (a) the practice of medicine; (b) the promotion of preventive medicine and the public health, and (c) the fostering of research and the increase of knowledge.

8. Medicine's chief concern must be for the individual physician; the service rendered by the individual physicians in the aggregate constitutes the great bulk of medical service. The quality of service which is given depends on the competency of the individual physicians who give it.

RIGHTS

9. The medical profession asks for its practitioners freedom of opportunity to develop to the limit of their individual capacities.

10. It asks a career of independence under conditions of free and dignified competition.

11. It asks remuneration sufficient for reasonable comfort for the individual and for his family.

12. Medicine has a right to control its own affairs. Its history of capacity and altruism justifies this claim.

In 1925 the State University of New Mexico conferred on Dr. Pusey the honorary degree of Doctor of Law, referring to him as "A man of the broadest attainments . . . who represents both the scientist's devotion to truth and the humanitarian's passion for the welfare of his fellow man." This was not idle praise. While serving as consultant to the health department of Chicago, Pusey and Belfield were responsible for the adoption by the city of the admirable Australian Act, by which physicians are required to report by code all cases of venereal disease. Chicago was the first big city in the United States to adopt this measure, a practical forward step in the campaign against venereal diseases. Dr. Pusey was a member of the advisory committee of the American Social Hygiene Association. He was consulted by the United States Public Health Service. He was a trustee of the Chicago Tuberculosis Institute. He participated in the affairs of the American Society for the Control of Cancer. Perhaps his most significant con-

tribution along this line was his participation in the plans for putting the work of the medical unit of the Red Cross in areas of disaster on a permanent basis. He had an active and leading part in the formulation of the plans which with minor changes are in effect today. "The man who feels this sentiment for humanity and who carries it out in his daily life, in his professional uses, and in his every contact with people, . . . the man who further devotes it to the betterment of his race without desire of reward, . . . this man is the rare sentimentalist" (Harvey P. Towle: Dr. Pusey, the Sentimentalist).

Not the least of his quasimedical services was the rôle that Dr. Pusey played in A Century of Progress. In 1929 civic leaders in Chicago began to plan the fair. Dr. Pusey was then a member of the executive committee of the National Research Council. The notice of his appointment, and with it a friendly word of appreciation, came over the signature of Prof. Albert E. Michaelsen. The National Research Council was established by President Wilson during the Great War to mobilize the scientific intelligence of the nation in order to stimulate research in the basic sciences and to encourage the application of them to agriculture, engineering and medicine to contribute to the general welfare. It was the successor to the National Academy of Science, established by President Lincoln. The council, largely because of the character of its members, occupied a unique position of trust in scientific circles. The directors of the centennial celebration wanted as the dominating theme of the exposition the services of science to humanity during the past century. It was a new and bold departure from precedents set by other expositions, and it was decided to try to induce the National Research Council to sponsor and to direct the activities.

"His [Dr. Pusey's] influence was of great value in our efforts to enlist the wise guidance and the powerful influence of this organization" (report of the president, Rufus C. Dawes, to the board of trustees). "Influence" meant meetings, conferences, travel and voluminous correspondence.

An executive committtee was appointed by the National Research Council; it consisted of Dr. Frank B. Jewett, president of the Bell Telephone Laboratories, Inc., Chairman, Dr. George K. Burgess, Gano Dunn, Dr. Vernon Kellogg, Dr. Max Mason, Dr. Michael I. Pupin and Dr. Pusey. "Never before, I believe has there been such a body of outstanding men devoted to the work of making clear to the general public the services of science" (from President Dawes' report). The indorsement by the National Research Council was of inestimable value, and Dr. Pusey's part in obtaining it was no small one. It was but his

first of many contributions to the success of A Century of Progress. He was a member of the executive committee of the board of trustees from the beginning of the fair. Early in 1928 he went to Mexico as special ambassador for A Century of Progress to cultivate the friendly interest and invite the participation of that country in the exposition, and Mexico did later contribute a valuable attraction. He was invited to go on a similar mission to Japan, China and the Philippine Islands, but other obligations made it impossible for him to take the commission. He was the constant companion and confidant of Rufus Dawes, and he was importuned by Mr. Dawes on frequent occasions to be host to visiting dignitaries.

His real service, however, was to medicine, for the medical section of the Century of Progress was organized under the direction of Dr. Pusey.

A plan was formulated which consisted schematically of three parts, first an exhibition of the sciences on which the art of medicine rests; second, one of the art of medicine; and third, one of the instruments and materials which are used in the science and art of medicine—the three parts to be integrated rather than sharply separated. And all should be developed so far as possible in a manner to show the history of their progress. The exhibit was to be kept from charlatanism, either professional or commercial. Medical leaders foresaw dangers. It was feared that the exhibit would get out of hand of scientific medicine and would be improperly commercialized. There was uncertainty whether a satisfactory popular exhibit of medicine could be made, and whether if made, it would attract visitors and be intelligible or useful to them. The plan was laid before the national medical organizations and it was concluded that it warranted professional support. Then came the task of enlisting the support of institutions and individuals who might furnish desirable exhibits. This was readily accomplished because an important factor in establishing confidence in the minds of the medical science exhibitors was the close personal relationship between Mr. Dawes and Dr. Pusey, which assured an ethically sound exhibit. Medicine, Dentistry, Nursing, Pharmacy, Hospitals and Veterinary Medicine had never before been represented as a health unit at any national exposition in America. How extensive was the exhibit is a matter of record. The medical section was one of the most popular parts of the exposition. It has been estimated that it was visited by more than 15 million persons, well over 80% of the visitors to the exposition. It was almost certainly the most successful undertaking of the sort to enlighten the public in the art and science of medicine that has ever been carried out (Eben J. Carey, chief of medical section, Century of Progress).

The exhibit was useful not alone to the public but to the medical profession also, for it led to a better comprehension on the part of the public of the problems that confront medicine and of its accomplishments. Pusey's guidance of the medical section of A Century of Progress was a truly great service to medicine, and it constituted a contribution of inestimable importance to the whole technic of public health instruction.

LITERARY WORK

It is plain that Pusey is no one-sided man of science—that he knows other things than dermatology. He is well versed in the history of Kentucky. Kentuckians generally are noted for their love of tradition, and Pusey's pride in his family tradition no doubt is the foundation for his hobby, the history of Kentucky. His "Wilderness Road to Kentucky," published in 1922, is an important document which historians consider will be a lasting contribution to the literature of the history of the South. The road, Daniel Boone's trail into the Kentucky wilderness, was for thirty years the main channel of communication between the seaboard states and the new settlements west of the mountains. Its origin antedates the War of Independence, and, curiously, in the literature there are only meager details as to its exact location. Pusey undertook to retrace the trail followed by the original pioneers. He began it as an interesting diversion but was soon so stimulated by the task that he continued the investigation over three years. Trips to various parts of the trail were made in 1919, 1920 and 1921. He rode over the entire length of the trail; he talked to old inhabitants, examined documents and made photographic records—a rare avocation for a busy physician. His report was in all respects—text, pictures, notes and maps—a treasure-house of information, written not only with accuracy but also with a vividness that made it interesting and readable, a quality that characterizes all his historical papers. "The Location of Martin's Station," "The Three Kentucky Pioneers," "Grahamton," "Early Textile Mills of Kentucky," and the other works of Dr. Pusey on the history of Kentucky all have an absorbing and vivid style. And each, aside from its interest, is a historical contribution of distinct value.

"The History of Dermatology" is the first history of that branch of medicine in the English language. His "A Doctor of the 1870's and 80's" is an account of the work of a country physician, without resort to fiction and as uncolored by romance as possible. As such it has historical value. "The History and Epidemiology of Syphilis," "The Importance of Being Historically Minded," "Noah Worcester," the address before the American Bar Association on "Fifty Years of Progress in Medicine," and other works written by Dr. Pusey are all significant additions to the literature of the history of medicine.

In recent years he has been content to leave the details of dermatology to the "younger generation in whose hands lies its future," while in his writings he acquaints the members of that generation with the accomplishments of their distinguished predecessors.

His "History of Dermatology" is likely to become a classic; it is stimulating and comprehensive without being a dull recitation of names and facts. Dr. Pusey makes of dermatology an inspiring story built about the personalities of real men and significant incidents about their discoveries. In his account of the history of syphilis, he said, "It is a dull man who can contemplate it without a thrill of enthusiasm." One can discern in all his medical historical papers a deliberate intent to give to the younger men some intimation of the interest and importance of the history of medicine, for "Younger physicians should light their torches at the fires of the ancients" (Rokitansky).

"The Importance of Being Historically Minded" is in a more editorial tone. It was his presidential address before the Institute of Medicine of Chicago in 1927. In it Pusey pointed out the changed attitude toward medicine; namely, that the science of medicine was being emphasized at the expense of the art, and that as a result there was being cultivated a false sense of values. Fifty years ago, the dominant conception was the importance of the practice of medicine. "That was regarded as the reason for our existence." A scientific foundation was necessary, and the importance of research was recognized. "The few men who by nature were intended for research—inevitably followed it in one way or another then, as now, although it was not exploited as the universal function of the medical man." With the great increase in knowledge in the past century there developed an active interest of mankind in general in health and, therefore, in medicine's problems, and with it the favor of philanthropy. Medicine indeed was making good use of the new opportunities. But,

> . . . in the flush of opulence and success there is no state of mind so difficult to maintain or so necessary for future success as humility. It is an act of wisdom, then, that we should be historically minded, in order to try to see ourselves in proper perspective, in order to take advantage of the wisdom, and especially in order to try to profit by the false steps of our predecessors; that we should scrutinize closely our state of mind; that we should realize as fully as possible exactly where we are, and what we are, and have no false exaltations. There has developed in medicine an attitude of superiority toward the accomplishments of the past, in fact the present period was referred to as the time since medicine has become a science.
>
> There is no time in history when medicine has not been accumulating facts, trying to systematize and coordinate them, to see them in their proper relations to find out the causes of things, and that is science.

Another false appraisement and a common one is that all that is worth while in medicine is science. "Medicine's business is quite as much with art. Science's concern is with facts and their interpretation. Medicine, on the other hand, is very much concerned with the practical application of facts." The danger, according to Dr. Pusey, was that

many members of the small group with a superior attitude toward the practice of medicine are at the source of supply of medical graduates and control the institutions of research.

> Is it not possible to have the art and the science of medicine in proper proportion? It is possible; that is what I am pleading for. . . . There is one glory of the sun, and another glory of the moon, and another glory of the stars; for one star differeth from another star in glory. . . . We should follow the scriptural wisdom of appreciating the glory of them all. Science has not all of it, and in emphasizing it at the expense of art we are cultivating a false sense of values in medicine and are failing to show, in evaluating ourselves and our function in the world, that important quality which, when applied to a consideration of the story of civilization at large, we call the quality of being historically minded.

This paper, perhaps more than any other written by Pusey, struck a responsive chord in the profession. He said things which physicians know and confess privately but which few say openly; he said the right thing in the right perspective.

"A Doctor of the 1870's and 80's" was inspired more by sentiment. It is the biography of his father, written as a tribute to a fine type of country physician of a past generation, and is dedicated to his mother, "who also served." Pusey has always considered his father the most important single influence in his life, and he feels that the ideals and philosophy which have become habit to him grew from the close association with, and example set by, his father, who placed emphasis on the substantial values in life. Pusey's grandfather had told him at an impressionable age that the man who lives for himself alone lives for a mighty scurvy fellow. From his father Pusey learned that the "main satisfaction of life comes through hard work which one enjoys" (Eliot). In this book he describes his father as a successful, hard-working practitioner who practiced his science with noble art. The story is lovely in conception and beautifully told. "It is a book that I would like to prescribe to every third year medical student as an obligatory part of his reading" (Harvey Cushing).

PERSONAL TRAITS

My association with Pusey began about nine years ago. He had already had his triumphs and was beginning to relax in dignified leisure. I can well recall my surprise the first time I went to his office. There was a large, dreary reception room with massive, uncomfortable mission furniture of another generation; on the bleak gray walls were numerous pictures, prints of the masters in cheap wooden frames, and prominently hung was a sign "Please do not smoke." In the center of the room, in everybody's way, there was a heavy wooden table with

many old magazines, all obviously chosen with an eye to Pusey's tastes rather than to the tastes of the patients! The room is essentially the same today. I was greeted by an austere gray-haired woman who has been in Dr. Pusey's employ for forty years and was then ushered into his private office.

His inner office was a delight. It is a perfect setting for "the well known country doctor of 7 West Madison Street" (Hektoen). It is a large corner room with wide frosted windows on two sides, which, with the high ceiling, give the room dazzling light. Pusey sat in a huge comfortable swivel chair before a wide old-fashioned roll-top desk. The wall over his desk was literally covered with small snapshots of relatives and scenes of his early life in Kentucky, and on another wall were photographs of many famous physician friends, most of them dermatologists. One drawer of the desk was open, and in it was hardware enough to furnish a small shop—all sizes and shapes of hammers, screw drivers, pliers, tape measures, nails—an accumulation of some forty years of "collecting." On top of the desk there was an array of about twenty pencils of different sizes and colors and more gadgets. Like that of so many potterers, Dr. Pusey's mechanical skill falls short of his aspirations. As we talked, he sat with his feet up on the desk, one pair of spectacles on his forehead, another low on his nose and several more pairs in his pockets, and he smoked incessantly, thin bitter little cigars. Behind his chair, on a book-shelf, there was a small old-fashioned iron urn which he used as an ash-tray. The urn is always in its place, so that as he sits back in his chair Pusey can empty cigar ashes into it without turning his head, and he never misses it. I was seated in the chair reserved for patients, a chair of his own design, a sort of operating chair, and a more uncomfortable one could not easily be conceived. In the corner there was an old-fashioned folding surgical chair, cumbersome and ugly. I soon learned, after several attempts to replace it, that it occupies a warm place in Pusey's heart. It was in the midst of his office hours that I called, and he invited me to stand by while he took care of a few patients. The first one, a middle-aged woman, had a small mole which required treatment with cautery. She was obviously used to "all things fine," and, with fear—it was more than apprehension—she asked if the procedure would be painful. "What if it is?" asked Pusey. She laughed a relieved laugh and told him to go ahead, that she just never had thought of it in that way.

Then there followed a man who wanted to know how long it would take to rid him of his eczema. Dr. Pusey replied that he couldn't say, as he was neither a prophet nor the son of a prophet—this was a favorite aphorism of his until a woman replied to it, after getting

her bill, "You may not be a prophet or the son of a prophet, but I'll say you're a profiteer." Another patient that morning was an important business executive who was consulting Dr. Pusey for the first time. Dr. Pusey sat him on a small low rickety stool the better to see the lesion on his forehead. The man looked up, smiled and said with a shake of his head, "By George, Dr. Pusey, you must be a damned good doctor to put patients on a chair like this." Pusey responded with his characteristic appreciative chuckles. It was all very confusing to me, for it was so different from the usual physician-patient relationship with which I was familiar. To top it all, however, his secretary, whom I had seen in the reception room, came in and delivered an impassioned rebuke because Dr. Pusey had neglected to do something that he was supposed to do. He bore it with assumed meekness. I was not long in learning that, as he said, such mornings were commonplace.

Frequently in the "after hours," when the last patient has gone, it is my privilege to sit with Dr. Pusey and listen to his delightful reminiscences. It is a privilege of which I shall always feel very sensible. Out of these experiences there has steadily increased in me, as in all who have been his associates, a sentiment of respect and boundless admiration for him as a man—a man with ideals who does not try to analyze those ideals but lives up to them. It was during these periods that I learned of his human qualities as an editor and of his intangible contributions to medicine.

Pusey became editor of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY in 1920. The predecessor of that publication, the *Journal of Cutaneous Diseases,* which had served American dermatology well before, was a good scientific journal but unfortunately lacked the financial support necessary to make it outstanding. Pusey induced the American Medical Association to take over the publication, an obligation which the American Medical Association might have been reluctant to assume because necessarily a specialized journal of that sort would be operated at considerable financial loss. His high favor and the reliance of the Association on his judgment were such, however, that the publication was undertaken, Pusey being appointed editor. The judgment of the Association was amply justified, for he gave to the ARCHIVES a vibrant personal editorship that has made it one of the foremost journals of medicine. As a dermatologic journal it ranks with the best in the world. He has given it intelligent editorship, perhaps because he is ever conscious of the responsibilities of the position. It is not a pleasant task for an editor to have to reject a paper that obviously represents hours of labor, but the interests of dermatology must come first. There is certain to be criticism when a mediocre paper is published, but those who criticize have no way of knowing

extenuating circumstances, as, for instance, that the author was dying of carcinoma and had never before written a paper. Or, if it seems that a report should have contained more data, perhaps Pusey knew that the operator was a man young in dermatology who had recently settled in a small community where there was no opportunity to obtain more data. And perhaps he reasoned also that the publication of the paper would help to establish that young man in his community, benefiting the author and fostering the ultimate good of dermatology. I can bear witness to several instances in which just such human considerations motivated Pusey's decisions. Usually, however, papers are considered objectively, the decision being uninfluenced by the personality of the contributor. Dr. Pusey is always open minded in his acceptance of new ideas. Many theories that are now established facts first found light in the pages of the ARCHIVES. His unusual combination of the ideal and the practical, a breadth of view that encompassed first hand knowledge of the sciences, the problems of the clinician and the needs of dermatology, a historical mind with the wisdom to appraise clearly contemporary activities, a strong individuality and exceptional executive qualities all combine to make him a singularly able editor with intelligent appreciation, "from whom one comes to expect an unusually kind comprehension of one's problems" (Stokes). By his editorship alone he has had a profound influence on American dermatology, and he has met his trust.

It is at medical meetings, however, that Pusey's personality is fully appreciated. I have never been present at any discussion in which he did not throw valuable light on the subject by some suggestion that went to the heart of the matter and pointed to the right course. He rises from his chair slowly and with some difficulty, for he is quite stout. He removes the little cigar from his mouth—and this is almost the only time he is without one. Attention is riveted on him. If his face slowly becomes wreathed in a smile and he fumbles to find room in his pockets for his spectacles, one is assured of a delicious aphorism or another example of his refreshing sense of humor. His voice is low and halting; the words are uttered deliberately as though chosen after careful thought. There are not quite the same ease and facility that he has in informal discussions with few listeners. He goes right to the point, however, in clear, understandable language; his southern drawl is more noticeable than usual, and the subject is summed up—the apt comment is made.

Recently at a national meeting the discussion centered about the propriety of the term precancerous. It was argued that the term is incorrect because all lesions classified as precancerous do not necessarily

become cancers. The discussion, though pedantic, was a live one and might have continued interminably had not Dr. Pusey, in his characteristic manner, remarked that he had known premedical students who never became doctors.

On another occasion a case of mycosis fungoides was being discussed. It was suggested that because mycosis fungoides is the cutaneous expression of several diseases of the lymph nodes the name should not be used. Curiously, there was acquiescence with this point of view until Dr. Pusey entered the discussion. The name mycosis fungoides should not be discarded, he said, because dermatologists

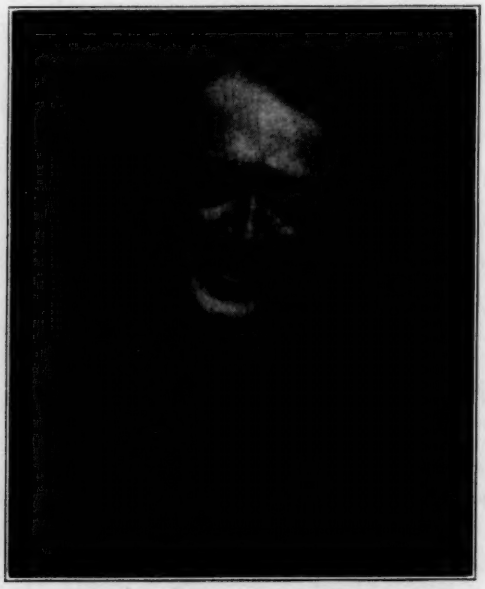


Fig. 3.—Wreathed in a smile.

know what the disease looks like and know what it will do, and if scientific exactness is going to be carried to a ridiculous end one might just as well stop calling a table "table," because, to be precise, it is lumber.

He does not limit himself to polemics, although when necessary he selects the best among the arts of the polemicist. Nobody is more ready with praise and encouragement for the novice, no one more appreciative of a case well presented and no one more ready to defend a discusser when defense is needed. I can well recall the first dermatologic meeting that I attended. A case of herpes simplex of the buttocks was presented because the condition had failed to respond

to the therapeutic ingenuity of the presenter. Several of the younger members seemed astonished that there had been any difficulty—they had always been able to clear up such disorders with simple measures. One member after another expressed agreement, to the obvious discomfiture of the presenter. Then Dr. Pusey dryly observed that in his experience cases of that condition were rare, that he could not recall when he had last seen one and that as he recalled the condition was particularly rebellious to any treatment he was able to give. Then several others of the older men agreed that that was their experience. I shall never forget the chagrin registered on the faces of the younger men. His authoritative experience and his pungency have many times cleared such situations and steered discussions to a straighter course. His comments are those of a mind that is essentially logical, and his conclusions are reasonable and honest. No one is more gracious to criticism or more open minded to opposing points of view.

It is always a stimulating experience to see a former associate or student of Dr. Pusey rise without hesitation to differ with him on a subject. There is no greater thrill than to witness these debates, and surely nothing can indicate more impressively his essential fairness and intellectual honesty. For his contributions to meetings, if for nothing else, American dermatology is indebted to Dr. Pusey.

The conduct of his office practice has not changed with the years. Since 1902 he has always had two and sometimes three physician assistants. He has ever been conscious of the value of an apprenticeship and has felt it his obligation to train younger men. He has made it his practice until recently to attach to his office staff a new young man every two years. The arrangements are interesting. The assistants are encouraged to develop their own practices from the beginning, and in addition Dr. Pusey pays them salaries sufficient for a livelihood. As the assistant's practice develops and his income increases, the salary is reduced. Actually the assistants have become his competitors from the start, and there are absolutely no restrictions to an associate's activities. When advice and consultations are necessary none of his assistants has ever felt any hesitation in asking his help. No contract is ever entered into; every arrangement is by gentlemen's agreement, and Pusey has always derived genuine pleasure in seeing his assistants get along. They have always felt free to leave his office whenever they thought it advisable, although he usually has suggested that they stay for at least two years of training.

Undoubtedly this sort of arrangement is better for a young man than the security of a salary, and apparently Pusey has always thought so. In the early years when he was in charge of the medical staff for an insurance company his younger brother had just settled in Chi-

cago to practice ophthalmology and much as he would have welcomed the remuneration resulting from an appointment as medical examiner for the company he was refused the appointment, for Pusey considered the work unsuitable for a man young in medicine—the rewards were too easy and the work was without responsibility.

His assistants have always participated actively in the management of his practice. When a patient comes to consult Dr. Pusey he is first seen by an assistant, who takes the history and makes the initial examination. Then Dr. Pusey comes in to confirm the diagnosis and prescribe treatment. When, as happens rarely, an unenlightened person objects to seeing an assistant, Dr. Pusey explains that he must be free to conduct his practice in his own way and that he assumes full responsibility for the acts of his staff. If the disorder is in any way unusual both assistants examine the patient with Dr. Pusey and then all retire into another room to discuss the case. If there is disagreement Pusey tells the patient so, and the psychologic effect of this is excellent. The patient comes to realize that the assistant's opinion is to be respected, and he learns too that he is in the hands of two or three physicians rather than of one. The patient derives benefit from the arrangement; certainly the assistant has an added incentive, and altogether Pusey has derived material benefit from this policy because the relationships between his patients and his assistants have always been such that Pusey has never felt obliged to stay at home when the spirit has moved him to travel.

Pusey maintains a laboratory and dispenses medicines to his patients. He did it, as his father did, when he practiced in Kentucky, and it may be that this influenced him to continue the custom. It has many advantages. The dermatologist uses ointments and lotions which usually require skill in their preparation, and they are better for his personal attention. As Pusey says, "An ointment depends as much upon who makes it as a biscuit." For the patient who prefers to have a prescription, he writes one. Intelligent patients have often expressed their satisfaction at having everything done in one office. With such a well equipped laboratory at hand there is an opportunity for experimentation, and Pusey's familiar calamine liniment, his epilating wax, his "baro" ointment and his modification of Unna's zinc oxide-gelatin dressing are the result of his dabbling in the laboratory. The usual laboratory procedures, serologic tests, urinalysis, blood counts and preparation of slides are all carried out in the office by a trained technician.

His therapy perhaps as much as anything else gives some insight as to Dr. Pusey's rationality. John Stokes has aptly commented on it:

> One of the greatest dermatologic therapists of this country has only five fundamental notes on his dermatologic keyboard. Perhaps we might extend them

to make an octave, but on this octave he can play symphonies. The expert dermatologist will never be superseded because into his employment of a small number of therapeutic agents there enters that indefinable quality of judgments and experience which is the art as distinguished from the science of our specialty. In this practice of the art Dr. Pusey is a master.

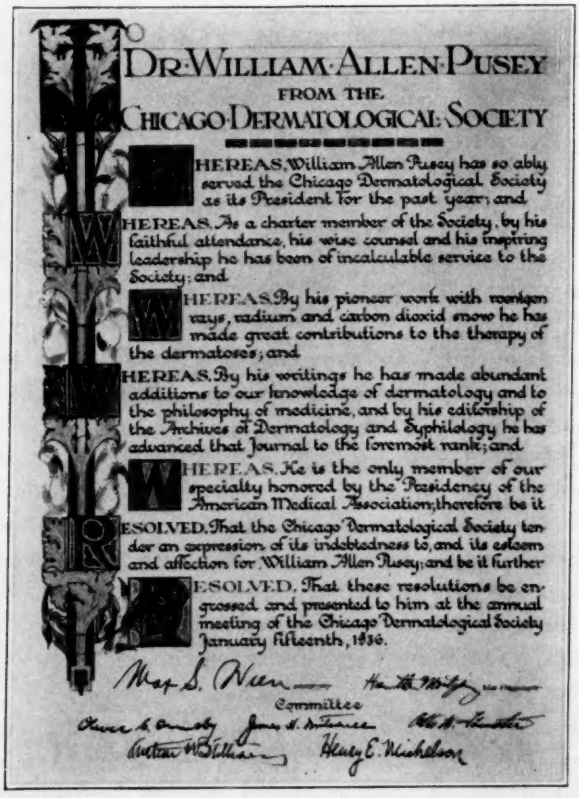
It is truly amazing how much Pusey does accomplish with a "bland ointment" and a "sensible diet." For a time in the early days of my association with him I was almost convinced that nothing more was needed to conduct a dermatologic practice, especially if I did not fail to "C. T." (continue treatments) when the patient was doing well, for "one cannot do better than to get better." His frequent use of a bland ointment is no doubt due to the fact that he early recognized the importance of external irritants in the production of inflammatory diseases of the skin. In his files one can find records of cases observed thirty-five years ago with the diagnosis "dermatitis irritant," and on the skins of the patients he rubbed a little of the suspected irritant, much as dermatologists do today in the modern patch tests. Pusey, as much as anybody, by his teaching is responsible for the present conception of the rôle of external irritants in eczema.

His "sensible diets" are even more characteristic of him. Almost every patient wants a diet, regardless of whether he has dandruff, ringworm or the itch. Dr. Pusey solemnly tells him, "eat like a sensible person, and if you find that something disagrees with you, don't eat it."

The combination of "bland ointment" and "sensible diet" has been responsible for any number of "miraculous" cures and has made for Dr. Pusey a host of everlastingly grateful patients. As he said in his recent address, "The Field of Dermatology," "cutaneous disorders often have the fortunate tendency to get well of themselves." Pusey recognized this early, and that is probably what Stokes meant when he said, "In this practice of the art Dr. Pusey is a master."

The question I am asked most frequently by medical acquaintances is "What is Pusey really like?" He has been a big name in medicine for so long that most younger men think him beyond approach. In fact he is cordiality itself, although there is about him a certain restraint that does not encourage familiarity. Pusey can be taken at face value. He is a man of temperament with occasionally a bilious mood, but there is nothing artificial or insincere about him. I have never known him to curry favor with anybody. Above all he is fair, and his fairness makes its impression on all who have contact with him. He has his foibles, even as do all mortals, and some of his idiosyncrasies are ludicrous. He is slow to shake hands, and if he can avoid it he never touches doorknobs or dirty money. He wears gloves summer and

winter, and he always carries a cane. On the golf course he carries an umbrella to shade him from the sun, yet he prefers to ride in his open car. He has a certain degree of vanity, and he is not obtuse to flattery, but he recognizes these weaknesses. He enjoys his ease and requires a great deal of service, which he accepts graciously. These are all perhaps traits of lesser importance that, if anything, make his personality the more interesting. His presence carries dignity—in looks,


DR. WILLIAM ALLEN PUSEY
FROM THE
CHICAGO DERMATOLOGICAL SOCIETY

WHEREAS, William Allen Pusey has so ably served the Chicago Dermatological Society as its President for the past year; and

WHEREAS, As a charter member of the Society, by his faithful attendance, his wise counsel and his inspiring leadership he has been of incalculable service to the Society; and

WHEREAS, By his pioneer work with roentgen rays, radium and carbon dioxid snow he has made great contributions to the therapy of the dermatoses; and

WHEREAS, By his writings he has made abundant additions to our knowledge of dermatology and to the philosophy of medicine, and by his editorship of the Archives of Dermatology and Syphilology he has advanced that Journal to the foremost rank; and

WHEREAS, He is the only member of our specialty honored by the Presidency of the American Medical Association; therefore be it

RESOLVED, That the Chicago Dermatological Society tender an expression of its indebtedness to, and its esteem and affection for William Allen Pusey; and be it further

RESOLVED, That these resolutions be engrossed and presented to him at the annual meeting of the Chicago Dermatological Society January fifteenth, 1930.

Committee

Fig. 4.—Testimonial of appreciation tendered to Dr. Pusey by the Chicago Dermatological Association.

in manner and in charm and conversation. He would have succeeded equally in any vocation he might have pursued. His career though full and interesting has been one of achievement rather than of adventure. Pusey has remarked that the nearest thing to a real adventure that be has had was that a few years ago he lost his pants in a Pullman car.

Dr. Pusey has given much to medicine, and he has gotten much from it. The material rewards have been more than sufficient. He

belongs to good clubs and enjoys them. His intimate friends are among the leaders in academic, civic, business, professional and social affairs. He is a member of "Room One Hundred," that small group within the exclusive Chicago Club which was described recently in the *Nation* as being more conservative than Wall Street. But above all he has sufficient of the durable satisfactions—the opportunity for intellectual excursions and the chance to be useful and respected in social and public relations and to satisfy ambition and pride.

Last year, when he retired as president of the Chicago Dermatological Society, the members tendered him a testimonial dinner. It came to him as a complete surprise, for he had attended the gathering thinking it to be the usual annual affair. When he was presented with a scroll of resolutions giving "appreciative expression to what is in our hearts and minds," he was visibly affected. As he rose to express his thanks, his lips trembled and his voice broke to such an extent that it seemed he might not recover himself. Occasions of this sort were not new to him. He has been the honored guest at impressive functions both in this country and abroad. He has heard himself lauded as a man of honor with high ideals, as a rare person who combines knowledge with philosophical humor, as a man of manifold achievements—a historian, writer, business man, loyal friend and companion, teacher, clinician, raconteur. He has been called a very human man, a leading physician with a combination of urbanity, scholarship and humor—honors that have fallen to the lot of few men. But none of the tokens of appreciation, I am certain, has he cherished more than that which was tendered him by his "neighbors."

EPILOG

Pusey, now full of years, is on the eve of his retirement from active participation in medical affairs. He has lately been indulging more and more in dignified, worth-while leisure; he takes a liberal amount of vacation, consisting usually in travel to interesting places, especially to Kentucky, where "new friends lend kind ears to my recitals." He can look back over a life which has been dedicated to what was at once a profession, an art and a career of service. Time has never hung heavily on his hands; he has worked hard at work that he has enjoyed. He has met his responsibilities.

If satisfaction comes to one for having lived a life of usefulness, Dr. Pusey should enjoy a large measure of it.

OFFICES AND MEMBERSHIPS HELD BY DR. PUSEY

Medical Societies:

Chicago Medical Society; President, 1918
American Medical Association; President, 1924
American Dermatological Association; President, 1910
Chicago Dermatological Society; President, three times
Institute of Medicine of Chicago; President, 1927
Chicago Society of Medical History
Chicago Pathological Society

Honorary Memberships:

Texas Dermatological Society (first honorary member)
State Medical Society of Wisconsin
New Hampshire Medical Society
St. Louis Medical Society
Societas Japonica Dermatologiae et Sifilographiae
Societas Dermatologica Austriaca, 1935
Societas Dermatologica Bohemoslovenica
Chicago Roentgen Society
St. Johns Hospital Dermatological Society, London (hon. fellow)
Alpha Omega Alpha

Corresponding Memberships:

Danish Dermatological Society
Dermatological Section, Royal Society of Medicine, England
British Association of Dermatology and Syphilology
Wiener Dermatologische Gesellschaft, 1931
Societas Dermatologica Hungarica
Société Française de Dermatologie et de Syphiligraphie

Miscellaneous Positions:

Member Executive Committee National Research Council, 1925-1931
Director Chicago Chapter American Red Cross
Trustee of the Museum of Science and Industry, Chicago
Trustee and member of executive committee, Century of Progress
Member Phi Beta Kappa

BOOKS BY DR. PUSEY

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ARGYRIA

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Although silver has been used as a medicine since ancient times, the first direct reference to argyria is that of Fourcroy [1] in 1791, which is as follows:

IV. Peculiar Effect of Nitrate of Silver in a Patient.

A protestant minister in the suburbs of Hamburg, suffering from an obstruction of the liver, took, on the advice of a quack, a solution of silver nitrate. After several months of this treatment, his skin gradually changed in color and finally became almost wholly black. Remaining so for several years, it then began to get lighter in color.

This observation, which was given me by M. Swediaur, is interesting, for it seems that the silver solution taken internally must act first on the stomach and then through all of the organs before being carried into the skin. It seems that the salt passed rapidly into the absorbent system. One would gladly follow further the course of this peculiar change in the skin.

Gager and Ellison [2] stated that Angelus Sala [3] in 1647 mentioned argyria, but I have not been able to find any reference to it, although he discussed the medicinal use of silver at some length.

Kobert [4] mentioned the warning given by Roncalli Paroloni (or Parolino) [5] in 1764 against too long continuance of medication with a gold or a silver preparation, but as I was not able to obtain the book, I cannot give the exact quotation.

Sala, Paracelsus [6] and other members of the alchemical school recommended silver especially for diseases of the brain and nervous system

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1. Fourcroy: La medicine éclairée par les sciences physiques, Paris, Buisson, 1791, p. 342.

2. Gager, L. T., and Ellison, E. M.: Generalized Therapeutic Argyria, Internat. Clin. **4**:118, 1935.

3. Sala, Angelus: Opera medicochymica quae extant omnia; frustulatim hactenus diversisque linguis excusa, nunc in unum collecta latinoque idiomate edita, Frankfurt, J. Beyeri, 1647.

4. Kobert, R.: Ueber Argyrie in Vergleich zur Siderose, Arch. f. Dermat. u Syph. **25**:773, 1893.

5. Roncalli-Parolino, F.: Humanum genus a veneris quotidianus liberatum, Brescia, 1764, cited by Kobert.[4]

6. Hermetic and Alchemical Writings of Paracelsus, translated by A. E. White, London, James Elliott & Co., 1934, p. 226.

because of its relation to Luna, who was considered to preside over these parts of the human anatomy.

From the middle ages until the middle of the nineteenth century the number of cases reported increased, but in the second half of the nineteenth century, as the faith in the value of silver lessened and the fear of its untoward action increased, argyria from therapy gradually became rare.

Allen stated this fact in 1906, in reporting a case of generalized argyria. This lull in the incidence of argyria was short-lived, however, for Crede in 1897 promulgated his theories about the wonderful effects of colloidal silver. Application of colloidal silver to the skin in the form of ointment was supposed to effect a cure of internal infections. This proved a false hope. It was found, however, that the colloidal forms of silver were valuable local antiseptics and because of the scarcity of free silver ions were only slightly irritating to mucous membranes. Denig as early as 1898, Pergens [8] in 1900 and de Schweinitz [9] in 1903 reported cases of local argyria resulting from the use of these new medicaments. Cases of generalized argyria appeared before long. Gaul and Staud [10] in their review collected thirteen cases of generalized discoloration reported between 1914 and 1928, in which the disorder had been caused by the organic preparations. In spite of this fact, as they bring out, the advertisers of the various forms of organic preparations of silver still stated that there was no danger of these preparations causing argyria. As a consequence these drugs are now household remedies, and the number of cases of argyria is increasing rapidly. Between 1928 and 1935, a period only half as long as the first, over twice as many cases—twenty-seven—were reported. Of these, one-fifth were in children under 10 years. One child, only 3 years old, was already blue, the pigmentation being due to silver used in its nose by an ignorant, overanxious mother. Fortunately, for so small a child the prognosis is fairly good. As a child grows the silver becomes distributed over a much larger surface and the pigmentation decreases (see page 73).

In addition, various forms of silver arsphenamine have been introduced for the treatment of neurosyphilis. There is no evidence that

7. Allen, R. A.: A Case of General Argyria, J. A. M. A. **47**:1829 (Dec. 1) 1906.

8. Pergens, E.: Argyrosis der Conjunctiva bei Protargolgebrauch, Klin. Monatsbl. f. Augenh. **38**:256, 1900.

9. de Schweinitz, G. E.: Argyrosis of the Conjunctiva and Lachrymal Sac Following the Prolonged Instillation of a Five Per Cent Solution of Protargol, Tr. Am. Ophth. Soc. **10**:161, 1903.

10. Gaul, L. E., and Staud, A. H.: Clinical Spectroscopy, J. A. M. A. **104**:1387 (April 20) 1935.

silver is particularly active against syphilis or that it has any more effect on the central nervous system than it has in any other portion of the body in which it has been deposited. An eminent pharmacologist [11] of an earlier day said:

> If one sees, from the internal use of silver nitrate, no action except the local effect, so one dare not expect any effect depending on action upon the nervous system. Experience in practice seems to corroborate fully this conclusion. One uses silver still in various nervous diseases, especially in epilepsy and progressive spinal paralysis, formerly also in chorea, mania and hysteria. This use originated, according to Libavius, from the time of the Kaballah in which one assumed that silver is related to brain disease as Luna is related to the brain.
>
> This nerve medicament has had a changing fate. While it is warmly praised by some physicians, others reject it as completely. For a time it lapses into oblivion, only to appear later. At present (1883) its use as a nerve medicament is decreasing; but will probably, as it always has, soon increase again.

About thirty years later this prophecy of Schmiedeberg was fulfilled in silver arsphenamine. It is hoped that the series ends here.

If the number of cases of argyria ceases to increase it will not be the fault of those interested in promoting the use of silver, for a new colloidal preparation of silver is now being introduced. The following statements are made in the introductory letter:

> The dispersed oxide will not produce argyria as far as clinical experimentation has determined. [The preparation] is completely non-toxic even when administered by way of the stomach in reasonably large doses and may be safely used in any case where a general disinfectant or antiseptic effect is desired.

ARGYRIA MAY BE LOCAL OR GENERAL

Localized argyria may be either of the tattoo form or of the smooth form. The tattoo form occurs on the face, hands and forearms of workers who file, drill, hammer, turn, engrave, polish, forge, solder or smelt silver and is due to minute particles of the metal driven into the skin and producing a spotted pigmentation. The smooth form is caused by silver solutions working into the skin through large or small wounds. This produces a pigmentation differing only in extent from the generalized form.

Generalized argyria may be caused by exposure in industry or by therapy, and the causes may be tabulated as follows:

1. Causes of argyria in industry
   (1) Sucking silver solutions into the mouth in the effort to suck them into glass beads to coat the inner surface (this corresponds to item 9)
   (2) Breathing silver-bearing dust
   (3) Putting fingers contaminated with silver dust into the mouth

11. Schmiedeberg, O.: Grundriss der Arzneimittellehre, ed. 2, Leipzig, F. C. W. Vogel, 1888, p. 276.

2. Causes of argyria in therapy
   (4) Absorbing silver from dental fillings dissolved by electric currents generated in the mouth
   (5) Absorbing silver from disintegrating sutures or tracheotomy tubes
   (6) Taking silver preparations by mouth for local effect on the gastro-intestinal tract or for an imagined general effect
   (7) Irrigating body cavities with silver solutions
   (8) Administering silver-containing drugs intravenously
   (9) Accidentally swallowing solutions used locally in the mouth, nose, throat or conjunctival sac

According to Harker and Hunter,[12] who recently investigated the silver-manufacturing industries of England, all objectionable practices have been eliminated from the industries of that country, except for the fact that dust is allowed to form in the packing of silver nitrate.

Item 9 in the foregoing list is the important one, and a long campaign of popular instruction will be necessary to overcome the urge of the laity for self-medication with silver.

DIFFERENTIAL DIAGNOSIS

In making a differential diagnosis in cases of generalized argyria the following considerations should be kept in mind: 1. In no other condition is there a bluish discoloration of the parts exposed to light while the rest of the skin remains ashy gray or even nearly normal in color (fig. 1). 2. In no other condition does a light spot result from an intradermal injection of a mixture of 1 per cent potassium ferrocyanide and 6 per cent sodium thiosulphate in distilled water. When argyria is complicated by pigmentation due to bismuth this test gives negative results.[13] 3. An amount of silver in the skin exceeding that corresponding to 8 Gm. of silver arsphenamine, as revealed by biospectrometric examination, establishes the possibility of argyria, though the change in color may not yet have occurred.

Few other conditions are likely to be confused with argyria. The common causes of cyanosis—cardiac, bronchial or pulmonary conditions—all present symptoms of the underlying difficulty. Polycythemia is evident in the blood count. In sulfhemoglobinemia and methemoglobinemia the color of the blood is strikingly mauve lavender to chocolate, while the serum has a normal appearance. The blood of persons with argyria is of normal color.

12. Harker, J. M., and Hunter, D.: Occupational Argyria, Brit. J. Dermat. **47**:441, 1935.

13. Spiegel, L.: A Discoloration of the Skin and Mucous Membrane Resembling Argyria, Following the Use of Bismuth and Silver Arsphenamine, Arch. Dermat. & Syph. **23**:266 (Feb.) 1931.

In Addison's disease the skin is brown, the pigmentation is not confined to the face, hands and forearms, the weakness of the patient is evident and the blood pressure is often low. Hemochromatosis is manifested by a general bronzing, the color being intensified by exposure to light, and hemosiderin and sugar are present in the urine.

Pigmentation due to bismuth resembles argyria closely. The blue discoloration in the mucous membranes cannot be distinguished from that of argyria. The color of the skin, while browner than the discoloration in argyria, is difficult to differentiate. Spectroscopic examination

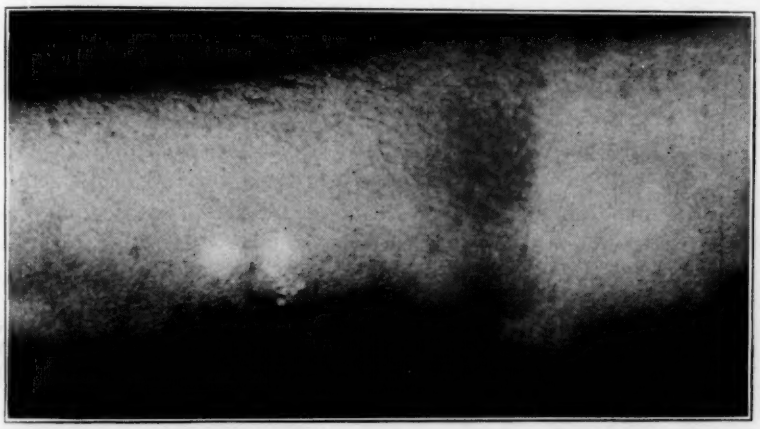

Fig. 1.—Forearm of patient with argyria showing sharp difference between the skin exposed to light and that covered by the sleeve and two depigmented spots produced by injection of reducing fluid.

makes it possible to differentiate between the two metals in the skin. The intradermal injection of reducing fluid does not clear the color when the pigmentation is due to bismuth.

ROUTES OF ABSORPTION

Though much time and thought have been spent in speculation regarding the exact way in which silver is absorbed into the body, no definite conclusions have been accepted by the majority of authorities. It is obvious that silver deposited in the tissues is colorless. In the upper part of the corium it becomes dark and appears as minute granules scattered in the papillary layer parallel to the basal layer of the epidermis, but in the sections which I examined it was not seen as a definite linear basal membrane, as some observers have described. This darkening is

assumed to be the result of the influence of light. In these parts the granules are often arranged in wavy lines that suggest elastic tissue fibrils.

Deeper in the corium groups of granules are massed about the outer root sheaths of the hair follicles and about the sebaceous glands, much as they are arranged in the papillary layer. About the coil glands, however, is seen a fine sharp line of brown granules forming a complete capsule around each group of glands. The darkening of these deeper deposits cannot be ascribed to the action of light but is thought to be due to some difference of the tissue fluids about the glands which darkens the granules.

In parts of the body subject to the influence of hydrogen sulfide from the intestines, a dark precipitate of silver sulfide is an easy explanation. Dark deposits in the kidneys, however, and in many other organs are harder to explain. Gaul and Staud's [10] quantitative estimation of silver in nonpigmented and pigmented portions of the skin and of the internal organs of patients with argyria shows that the colorless form of silver must be permanently deposited in all the connective tissue, turning dark nearly everywhere except in the covered portions of the skin.

There has been some difference of opinion regarding the presence of particles of silver within the cells. Silver has been observed in endothelial cells, in cells in the lymph glands and in the Kupffer cells of the liver. It would be strange indeed if such foreign particles were not taken up by the phagocytes. While their presence in these cells suggests their relation to the reticulo-endothelial system, Zoon [14] expressed the belief that Blaschko's experiment with potassium hydroxide showed that they are not in the *Gitter Fasern* of the skin but in the elastica.

To satisfy my curiosity, I submitted three specimens of my skin to Dr. L. E. Gaul for biospectrometric examination. An area of normal skin taken from above the knee contained an amount of silver corresponding to that contained in 8 Gm. of silver arsphenamine. How I acquired so much silver, I do not know, unless it was derived from amalgam dental fillings which I wore for a number of years. Skin from an area into which mild protein silver had been injected showed an amount of silver corresponding to that contained in 10 Gm. of silver arsphenamine, while skin from a patch which had turned pale as a result of injection of reducing fluid contained the same amount of silver. The amount removed by the intradermal injection was therefore small, or possibly the silver was redeposited before it left the deeper part of the area.

14. Zoon, J. F.: Ueber histologische Befunde bei Argyria cutis, Dermat. Ztschr. **70**:125, 1934.

TREATMENT

Albers,[15] the first English writer on the subject, reported that treatment with dilute sulfuric acid and dilute nitric acid internally combined with baths of different kinds was not successful.

Yandell,[16] the first author to discuss this subject in American medical literature, had two patients with generalized argyria caused by the internal use of silver nitrate in the treatment of epilepsy. Both acquired syphilis and were treated with mercury vapor baths causing profuse sweating. This was followed by internal administration of potassium iodide. One patient had to discontinue using this drug, "because of its disagreeable effects"; the other persisted "until all traces of syphilis had passed away." The skin of the first became lighter; that of the other, which had been "much the darker of the two," improved until there was "not a shadow of the disfigurement." His weight increased about that time. The improvement in color may have been due to this fact, as Warthin recorded in his case of argyria, in a boy.[17] Warthin's case is interesting:

> An undersized, puny boy of 14, who was anemic, was treated for chronic ulcerative colitis for eighteen months by daily irrigation of the colon with a 1 per cent solution of silver nitrate. Nine months after the treatment was started his skin and mucous membranes were slightly discolored. This discoloration progressed until it became marked. The cure of the colitis resulted in rapid development and gain in weight. Six years later the patient was stout and his skin had become much lighter. A fixed amount of silver had been distributed over a larger area.

The treatment with potassium iodide described by Yandell has been tried by many others with no success. However, Schwarz,[18] in 1911, used potassium iodide in a saturated, in a half saturated or in a 33 per cent solution in water, injecting the solution under the conjunctiva as superficially as possible. His idea of local superficial injection of a solvent antedated the method which my co-workers and I used, although we did not know it at the time we first used that treatment. He injected 3 or 4 minims (0.18 or 0.24 cc.) in one spot. If the area is large and

15. Albers, I. A.: Observations on a Change of Colour in the Skin Produced by the Internal Use of Nitrate of Silver, Med.-Chir. Tr., London **7**:284, 1816.

16. Yandell, L. P., Jr.: Cyanosis from Nitrate of Silver Removed by Iodide of Potassium, Am. Pract. **5**:329, 1872.

17. Warthin, A. S.: Argyria, in Buck, A. H.: Reference Handbook of the Medical Sciences, ed. 4, New York, William Wood & Company, 1923, vol. 1, p. 527.

18. Schwarz, L. E.: Method of Decolorizing the Conjunctiva in Argyrosis, Ann. Ophth. **20**:223, 1911.

the reaction slight, another injection may be made as far as possible from the first. Two or three weeks after the reaction has subsided the treatment may be repeated at other points. The color fades slowly. This seems to be reliable evidence that potassium iodide does have a slow action on silver deposited in the tissues. Whether a preceding treatment with mercury, as given by Yandell, made the action of the iodide more effective may well be considered.

Crispin,[19] in 1914, tried potassium iodide without benefit. His patient had acute coryza and was given 0.6 Gm. of methenamine by mouth three times a day. Her pigmentation began to fade at once.

Olson,[20] in 1917, reported a case of localized argyria resulting from the use of mild protein silver in the conjunctival sac of a patient with a fractured nose. Olson made from fifteen to twenty injections of solution of mercury bichloride into the pigmented area with slight result. Two years later, following Crispin's suggestion, Olson gave his patient 0.6 Gm. of methenamine by mouth three times a day. In two weeks half of the pigmented area had disappeared. When he gave injections of methenamine to animals which had previously received injections of mild protein silver he did not succeed in clearing the color of their tissues.

Cannon [21] treated two patients with argyria caused by silver arsphenamine and one with discoloration resulting from the use of mild protein silver with sodium and calcium thiosulfate. After that treatment had been given for a year he claimed that there was a marked decrease in the intensity of pigmentation. The drug was given orally and intravenously.

I [22] administered sodium thiosulfate orally and intravenously in large doses for one month without noticeable result. I then gave methenamine intravenously for a month without definite result. Friends of the patient congratulated her, asserting that they noticed a definite improvement in color. A judgment as to improvement of

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19. Crispin, A. M.: Argyrism Following the Use of Collargol, J. A. M. A. **62**:1394 (May 2) 1914.

20. Olson, G. M.: Argyria Localis Due to Organic Silver Preparations, J. A. M. A. **69**:87 (July 14) 1917.

21. Cannon, A. B.: Value of Silver Arsphenamine in Treatment of Early Syphilis, J. A. M. A. **102**:268 (Jan. 27) 1934.

22. (*a*) Stillians, A. W., and Lawless, T. K.: An Intracutaneous Method of Treating Argyria, Arch. Dermat. & Syph. **17**:153 (Feb.) 1928; The Intradermal Treatment of Argyria, J. A. M. A. **92**:20 (Jan. 5) 1929. (*c*) Stillians, A. W.: Argyria: The Practical Value of Its Endermic Treatment, Report of Eighth Internat. Cong. de Dermat. & Syph., 1930, p. 714.

argyria from the color of the skin must be made with great caution, for without a control one is easily misled by changing light and changes of circulation in the skin. A card or plaque painted to match the skin of a certain site at the onset of treatment will afford a valuable means of control. The patient whom I treated had such control observation, and the result was wholly satisfactory. It was this comparison that enabled me to state definitely that no change had taken place after two months of treatment. Harrop, Weinstein, Soffer and Trescher [23] in studying the pigmentation in Addison's disease during treatment have found this method to be the only reliable control.

Dr. Lawless and I acknowledge that these trials, because of financial considerations, were too short; still they were longer than the treatment which Crispin and Olson thought sufficient for cure. Longer tests, controlled by the method of Gaul and Staud [10] should be made of these methods of internal treatment. As we stated in our first article,[22a] however, it is entirely possible that the skin, because of the action of light, will be the last to release its silver deposits. When one contemplates the comparatively enormous amount of silver in the body, one realizes that, unless the solvent is a quick acting one, it cannot clear the whole organism rapidly enough to cause a return of the skin to a normal hue within any reasonable time. Therefore we used a local treatment, injecting intradermally a photographic reducing solution containing 1 per cent potassium ferrocyanide and 6 per cent sodium thiosulfate into an area of localized argyria. Each injection of the reducing fluid left a light spot, the area becoming nearly as pale as the normal skin. By treatment consisting of many injections of the reducing solution the whole anterior part of the patient's face was cleared, as shown in figure 2. The lower eyelid was the only part in which the result was not satisfactory.

Since then we have had the opportunity to treat several patients with argyria localized in the lower lid and have obtained only slight results. The skin is so thin in that region that the injected fluid does not come into proper contact with the superficial deposit of silver. A good proportion of our patients have asserted that they were satisfied with results, although every effort was made at the outset to explain to them the limitations of the treatment in that area. The contrast with the normal lower lid of the other eye is too striking for any but a perfect result to be satisfactory.

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23. Harrop, G. A.; Weinstein, A.; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatment of Addison's Disease, J. A. M. A. **100**:1850 (June 10) 1933.

In conjunctival pigmentation, however, the success has been brilliant. Weymann,[24] who first applied the method to this tissue, was consistently successful. Prof. Sanford Gifford told me that his results with the treatment as modified by Weymann have been excellent in several cases.

So far cure has been reported in only one case of generalized argyria besides that observed by Dr. Lawless and me. Shimizu [25] had a satisfactory result. At first he tried a treatment with sodium thiosulfate; he gave the patient one hundred and sixty intravenous injections during eighteen months, but no improvement except slight lessening of the color of the nail beds resulted. He then tried intravenous injections of a mixture of 7 cc. of a 10 per cent solution of sodium thiosulfate and 3 cc. of a 10 per cent solution of potassium ferrocyanide every day for six weeks without any benefit. Subcutaneous injections of this mixture were likewise without result. Intradermal injections, however, had a prompt effect. After four months of treatment, the face, neck, chest and shoulders were practically normal. He emphasized, in a private communication, the beneficial effect of treatment on the morale of his patient, who before treatment refused to mingle with others or even to go out on the street because of her disfigurement.

The method is slow, it is true, but it is no more so than the treatment of extensive hypertrichosis with electrolysis, and the results are prompt and striking. While my co-workers and I, of course, feel that this method of treatment may bring great benefit to the patient with argyria, we acknowledge that the only ideal treatment of argyria is prophylaxis. A campaign should be waged by the medical profession against the unguarded use of organic preparations of silver, especially against the use of such preparations as a household remedy. Contemplation of the fact that ever since 1898 warnings have been given of the danger of long-continued use of colloidal and organic preparations of silver and that the use of these preparations in medicine and as household remedies has steadily increased in spite of these warnings does not offer much hope that anything but a vigorous campaign will bring results. The discovery of efficient and nonirritating antiseptics not containing silver and suitable for use in the nose and throat would simplify the problem. Physicians

24. Weymann, M. F.: Argyrosis of the Conjunctiva: Its Successful Treatment, J. A. M. A. **93**:1367 (Nov. 2) 1929; Argyrosis of the Conjunctiva, Tr. Am. Ophth. Soc. **30**:538, 1932.

25. Shimizu, K., Ueber einen verheilten Fall von Argyria cutis universalis, Nogoya J. M. Sc. **9**:175, 1935.

who feel it necessary to treat chronic disorders with silver compounds should employ the Gaul and Staud test to guard against excessive dosage. Harker and Hunter reported the great improvement in industries using silver. Nearly all the dangers have been eliminated. The problem is now squarely up to the medical profession.

Dr. Albert Sternthal helped me translate Sala's difficult medieval Latin.

104 South Michigan Boulevard.

NOTE.—The colored plate, figure 2, omitted from this issue, will be incorporated in the reprints.

NEW ARSPHENAMINE SYNTHETICS IN TREATMENT OF SYPHILIS

A CONSIDERATION OF TEST PROCEDURE AND OF A NEW DRUG (TRIARSEN)

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PHILADELPHIA

I. GENERAL PRINCIPLES FOR EVALUATION OF DRUGS

The versatility and resourcefulness of the organic chemist and the enterprise of the pharmaceutic manufacturer have developed within the past fifteen years a plethora of synthetics and forced on clinical and laboratory organizations a new subdivision of activities, that of clinical testing of drugs. With this type of study and responsibility we have now had a little more than a decade of somewhat variegated experience,[1] and since the literature from the standpoint of organization and

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1. We are singly, or as co-authors, responsible for clinical investigations (in a number of instances as first or introductory publications) of the following drugs: tryparsamide, sulfarsphenamine, bismuth sodium tartrate, bismuth arsphenamine sulfonate (sulfarsphenamine bismuth), dihydroxyanthranol and triarsen (Stokes, J. H., and Wilhelm, L. F. X.: Tryparsamide in the Treatment of Neurosyphilis: A Study Based on Observation of One Hundred and Fifty-Two Patients for Eighteen Months, Arch. Dermat. & Syph. **11**:579-609 [May] 1925. Stokes, J. H., and Behn, C. W.: Serologic and Clinical Results in Various Types of Syphilis with Sulpharsphenamine Administered Intramuscularly, J. A. M. A. **83**: 242-246 [July 26] 1924. Stokes, J. H.: Bismuth Sodium Tartrate, unpublished data. Stokes, J. H., and Chambers, S. O.: Bismuth Arsphenamine Sulphonate: Clinical Observations on a New Arsphenamine Synthetic in the Treatment of Syphilis, J. A. M. A. **89**:1500 [Oct. 29] 1927. Stokes, J. H.; Miller, T. H., and Beerman, H.: An Appraisal of the Newest Arsphenamine Synthetic, Bismarsen, in the Treatment for Syphilis, Arch. Dermat. & Syph. **23**:624-641 [April] 1931. Beerman, H.; Kulchar, G. V.; Pillsbury, D. M., and Stokes, J. H.: Dioxyanthranol 1-8 as a Substitute for Chrysarobin, J. A. M. A. **104**:26-28 [Jan. 5] 1935).

technic is scanty [2] and the need for systematization and review of the field apparent, we undertake in this paper (1) to discuss the general principles which seem to be applicable to this form of clinical and laboratory activity and (2) to present a new drug for its intrinsic interest and possibilities and as illustrative material. The discussion is confined to the field of antisyphilitic and especially arsphenamine medication, though some of the comment may well be applied to other fields.

CURRENTLY RECOGNIZABLE DIFFICULTIES

The finding of one's way through the jungle of drug testing has been a matter of trial and error and of sometimes discouraging and humiliating experience. Enterprise dominated by experience rarely begins with altruistic preliminary organization; so for years it is likely to be characterized by lack of "code" or principle—every man for himself from discoverer and originator to manufacturer and marketer. The tender minded will be offended and the unsophisticated trodden on, betrayed or exploited. From this "scrimmage era" will emerge a group of pessimistic souls who, having seen the worst and felt it, will thereafter hold all savor of the "commercial" as abomination itself and will rate all who have had contact with it as without caste and untouchable if not actually given over to malefaction and richly deserving of opprobrium. Such censorious persons forget that technical enterprise and organization can have honorable standing and be carried on by persons sincerely interested in progress and distinguished achievement even though they earn a livelihood directly from that progress. The pessimistic product of the "scrimmage era" will be the die-hard element in any medical movement for internal reform: a critical, distrustful and surveillant group, a police contingent of the school of "if you see a head, hit it," who will have none but a growl of suspicion for any and every manufacturer's label. The existence of such a group is the inevitable result of invincible distrust aroused by admittedly distrust-deserving tactics in ultradistrustful minds. With this group the manufacturers must expect to have to bear as a punishment for their sins, while with exemplary conduct and more than average cooperativeness of mind they seek for and respond to the best that the situation demands of all concerned in it. If the majority of manufacturers and their technical aids and staffs persist through cuffs and rebuffs in an unfailing disposition to meet every scientific and idealistic requirement, and if among themselves or with the aid of external disinterested agencies they reduce and curb the competitive forces and utilize the cooperative possibilities of their fields, there is every reason to believe that scientific creation,

2. Stokes, J. H.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1934. Snodgrass.[5]

technical excellence, economically profitable preparation and adequate intelligent clinical testing of synthetic drugs can be made a unified and controlled activity. A lack of code can then be superseded by cooperation, fair play and rapid economical progress for all concerned, from synthesist to patient. That the difficulties which confront one in the field of manufacture, testing and utilization of drugs are shared by other if not by all fields of combined scientific and technical accomplishment must be both apparent and consoling as one watches the evolutionary process in other domains besides that of medicine. The outstanding obstacles to successful transition from an era of "no code" to one of "code," as we have observed them, are as follows:

1. The excessive influence of sales organization, business expediency, competitive tactics and point of view on the study, manufacture and introduction of synthetic drugs.

2. The costliness of the scientific or laboratory phases of a test of drugs—synthesis and testing and experimentation on animals. Under the domination of competitive business regimens something must by hook or crook be gotten from the public to pay for what does not, as well as for what does, prove useful and salable.

3. The disposition to underrate the responsibilities, difficulty and expense of clinical testing and hence to secure the cheapest evidence possible—that of the inexperienced user of a few samples—as the basis for a sales campaign in place of the more costly, but vastly more valuable, study of an expert under proper conditions of organization and control.

4. The varying degrees of nontransmissibility of the results of tests of toxicity and chemotherapeutic efficiency in animals to the field of clinical toxicity and clinical results in man.

5. The inadequate exchange of experience and point of view between laboratorians on both the synthesizing aspect and the tests on animals with each other and with the clinical ester of drugs. A laboratorian may be a competent judge of reactions in animals while being deficient in adequate knowledge of the clinical problem in man and, less often, vice versa.

6. The time-consuming character of adequate clinical research in action of drugs. Especially is this important in the form of delayed return on high investment costs and of large risk of ultimate failure in the field of antisyphilitic therapy. Toxicity for animals may be determined in days or at most in a few weeks; therapeutic effect in animals may be ascertained in weeks and months; determination of toxicity including reactivity in man requires months, and ultimate therapeutic effect in man is ascertained only in years.

7. The excessively surveillant and distrustful attitude toward manufacture, carried forward from the worst experiences of the "scrimmage era" and still maintained by some referees. Where existing authorities have moderated this reaction they too often still maintain an aloofness and an attitude of implied taint and noli me tangere which is noncooperative if not antagonistic and obstructive.

8. The lack of defined and controlled procedure in clinical as distinguished from laboratory testing of drugs.

9. Nonrecognition of personal equational elements in test work and failure to safeguard against them.

10. The disposition, under pressure of sales expediency and natural enthusiasm, to overexpand and ballyhoo rather than precisely to define and evaluate the field of a drug.

COMMENT ON THE OBSTACLES

It is certainly to be regretted in many ways that the development of scientific knowledge and the practical introduction of therapeutic agents into medicine should be so exclusively controlled by private competitive enterprise. The money-making motive and acquisitive ethics form a poor background for idealistic achievement in such a field. The edge which business competition, particularly the vicious intensity of high pressure salesmanship in American business life, puts into production, marketing and sales, while it may carry some advantages under the guise of a stimulating effect of rivalry on thought, costs altruistic effort a great deal in warped and prejudiced point of view, exaggeration and distortion of both good and bad, foisting on the one hand and suppressing on the other. The forcing of ineffectual remedies onto the market, the unscrupulous advocating of dangerous procedure, the glossing of defects and exaltation of merits, the multiplication of drugs with substantially identical effects and the failure of synthetics of distinct value to win recognition because they have not been sufficiently written or talked up can be illustrated without difficulty from current practice. Just as every publisher feels he must have a book in a certain field on his list and every manufacturer a car of certain type, so every manufacturer and marketer of pharmaceuticals must have a drug to fill a certain place in his "line." In the field of the arsphenamines this state of affairs has led to costly reduplications ultimately scrapped almost completely by long time adverse experience. A conspicuous example is sulfarsphenamine, which one of us (J. H. S.) was one of the first to investigate clinically.[1] The drug was endorsed by a laboratorian of high rank in this country (Voegtlin [3]), and its low toxicity for ani-

3. Voegtlin, C.; Johnson, J. M., and Dyer, Helen: Sulpharsphenamine: Its Manufacture and Chemotherapeutic Properties, Pub. Health Rep. **37**:2783-2798 (Nov. 10) 1922.

mals, its low storage and rapid elimination and its therapeutic effect all seemed most promising. It invited a return to an era of intramuscular medication, simpler and more effective than intravenous procedure. Its clinical testing and evaluation, however, illustrated ideally the variables and the lethal mutant factor—to borrow terminology from genetics—which a new drug carries as the unknown x in its future. Sulfarsphenamine fell short because of differences in reaction-producing effect and toxicity in animals as compared with the effect and toxicity in man—a difference which neither its laboratory nor its clinical sponsors could at the time foresee—injury to the hematopoietic system producing purpuric and hemorrhagic complications and injury to the complex mechanism of vascular, cutaneous and allergic reactions involved in exfoliative dermatitis. Not only did its unpredicted and perhaps unpredictable reaction-producing quality in man practically nullify its clinical usefulness despite its impeccable laboratory credentials, but its therapeutic efficacy was endorsed on the one hand and damned on the other in a way that well illustrates not only how many factors enter into a therapeutic evaluation but how inevitably personal equation must warp even the most conscientious judgment. There was reason to believe not only that sulfarsphenamine is, like neoarsphenamine, a variable substance, differing from lot to lot and from manufacturer to manufacturer but that its effectiveness varies radically with the route of administration. Administered intravenously it is certainly not the same drug that it is when administered intramuscularly. A competent observer once regarded its presence in certain foreign preparations as the explanation of the enormous dose of those drugs which could be tolerated by patients, while its relatively low therapeutic efficiency by the intravenous route led to the rejection by a high referee of arsenicals in which it forms a principal ingredient. The example of sulfarsphenamine should serve as a lesson to chemists and laboratory testers, on the one hand, and to clinicians, on the other, on the complexity of the field with which they deal.

It is regrettably in accord with expectancy that the more a competing concern specializes and makes commercially remunerative a certain type of drug, the stronger will be the impulse and the determination on the part of another to invade and capture a portion or all of the field. Sales competition by ballyhoo inevitably results in manufacturing practices such as those described in the following paragraphs, of which we have seen examples in the past decade.

The effort to combine speed and numerical impressiveness in a test by increasing both the total number of injections given and the number of users by a process of small sampling without adequate regard for the competence and critical judgment of the testers or the criteria of effectiveness which they are likely or able to use is a leading

fault in present practice. It is possible to announce thousands of injections within a short time if the spread of sample distribution has been sufficient, yet no one observer has had the opportunity to evaluate either the ultimate toxicity or the ultimate therapeutic effect of the drug. A report on immediate reactions, for example, assumes one color when patients are critically watched by a single trained observer on a closely controlled service and an entirely different color when they are viewed by an inexperienced person who gives here two and there six injections with no follow-up or investigation of the causes of lapse. Unless, therefore, a manufacturer indicates clearly the authoritative auspices and the respective volumes of the reports on which he bases his sales campaign, he is dropping back to the "I had a case" method of evaluation in fact, while in public appearance he pretends the validity of systematic volume control and capitalizes on the American weakness for size and number. The "spreading" of small samples by a large organization of detail men to increase aggregates of treated patients for ballyhoo purposes, furthermore, makes it impossible to evaluate lot variations intelligently. One of the most experienced and distinguished of European dermatosyphilologists (Bloch [4]) confirmed at once the impression of one of us (J. H. S.) that lot variation, especially in the early months and years of a drug employment, is a matter of critical concern. He was repeatedly obliged, for example, to wire the concern with which he was working on certain compounds to withdraw given batches from the market, while others proved effective and safe. One of us (J. H. S.) has known the entire clinical program for a carefully studied arsenical in a clinic of high rank to be canceled as a result of pain and local reaction to the first half-dozen injections, while another clinic of equal experience and competence proceeded to give hundreds of injections of the same drug without a serious by-effect. Such elements are parts of an undesirable impressionism and a personal equation factor of error that is inevitably multiplied by multiplication of observers. It is by no means necessary or wise to confine testing to a single observer, but the number of fully equipped and competent observers is limited, and the attempt to rush a drug into use by spreading the testing through mere numbers of uncritical users is bad practice.

The technic of the person administering a drug of the arsphenamine series is in itself an important element in test procedure. The variability introduced into the behavior of a drug by concentration and dilution, by oxidation, by speed of administration, by preparation and by after-care of the patient is appreciated by relatively few of those included in an indiscriminate sampling campaign for a new preparation. We have had reason to believe not only that the factors are of importance

4. Bloch, Bruno: Personal communication to J. H. S.

but that less tangible elements, fear-induced reactions, suggestion and personal warp on the part of the therapeutist, can influence the effect or the apparent effect of a drug in man. While spreading of the testing over a small selected group of investigators using uniform procedure tends to diminish eccentricity, technical error, personal bias and wishful thinking as factors in false evaluation, the indiscriminate distribution of a drug to mere numbers of inexperienced users and observers multiplies these sources of error manifold. It would appear, then, that an essential to good practice in drug testing is the abandoning of sampling campaigns and tests by small users with limited or no experience and the adoption of mass testing under specially experienced observers with special equipment and special facilities for interpretation. It will then be possible to use both uniform and varied procedure under proper conditions of control.

Who shall be the judge or the selector of those chosen for a clinical test of a drug? In the past decade we have observed at one time or another the following procedures forming an evolutionary sequence. At the outset the sales department of a manufacturing concern used its most plausible and insinuating representatives to "introduce" a drug (usually in exchange for a supply gratis and promise of more to come) into clinics the personnel of which was eager to try something new and to score a scoop by early publication of results. It is, of course, a considerable help both to budget and to publicity to lead a winner onto any field, and who has not felt the urge to "see what there is in it"? A second method is for the synthetic chemist or pharmacologist to approach clinicians of his acquaintance or to use the lists or clientele of the concern undertaking the manufacturing responsibilities in selecting testers for his preparation. A third method is for the manufacturer, either directly or through the synthesist, to establish in advance and perhaps in connection with other fields of work a research liaison with a clinician or investigator of reputation and to use his help in working out the applications of new drugs. This service may be obtained gratis as a part of state or governmental check responsibility, as a part of connection with a potent official agency, such as the Council on Pharmacy and Chemistry of the American Medical Association, or by the establishment within the testing investigator's organization of a supported research project, a part time or a full time fellowship for the more or less disinterested study of the clinical problems involved.

The defects of the first method are obvious. A sales manager is no judge of scientific or clinical competence. His tactics are subversive in that his appeal is to lower rather than to higher motives in those he approaches. He exploits the altruism, let us say, as well as the self-interest of those who accept him. The guileless among them presently find that dealing with an organization (sales) which by hook or

by crook must make out a case for itself and its product leads to pressure for early reports and the soliciting of unauthorized interviews with technicians and minor assistants, followed by premature, improper and misleading or misquoted citations and use of their actual or alleged utterances. The good name of the testing organization is exploited from the start—"so and so is using our product"—and, whether in a rush of enthusiasm or in actual falsification, the statement is added "and has had excellent results." A good deal of subtlety, against which no one, we venture to say, is entirely proof, especially if it is flattering, goes into the "bagging" for manufacturing organizations of the leading testing groups of the country. But it may be safely offered as a maxim that the mere shadow, not to say the actual sitting in, of a sales representative on any part of the preparation or set-up for clinical testing should warn the tester of trouble and possible discredit to come, and that reasonable evidence that the sales organization constitutes a hypertrophied division of the technical or manufacturing organization, to say nothing of evidence that salesmen are "prying," advising personnel, applying pressure or prematurely propagandizing, should be cause for withdrawal from, or avoidance of, a project.

The clinical investigator should, then, demand from the outset direct contact with the responsible head of the manufacturer's scientific organization. The determination of toxicity and therapeutic efficiency for animals as well as adequate chemical control of manufacture and distribution is thus far at least his business, and the varying degrees of governmental control exerted over his product should not be accepted as substitutes for proper equipment and controls within his own organization. None the less it may be pointed out that much reduplication of effort can occur at this point. To the clinical investigator the laboratorian and chemist should supply full information not only as to the general chemical characteristics but as to the results of tests on animals. It is a great satisfaction today, after the old "sales organization era" of approach, to find oneself dealing directly with a scientific man possessing a comprehension of controls, time factors, expense and labor, an intelligent appreciation of judgment and experience and familiarity with the ethics of scientific reporting and evaluation. Great though the advance marked by this form of direct cooperation has been, it is still evident that scientists on the technical side suffer occasionally from competitive and commercial pressure factors; they must indeed make their establishments earn their keep, somewhat as faculties are sometimes made to earn their keep under publicity bureaus and pressure by means of reprint lists. The tendency to translate experience with tests on animals directly into experience with tests on man still persists, and there is some tendency to discount hazards and problems which because they have not been recorded or evaluated in

animals are discounted or overlooked in man. The only remedy for such situations seems to us to be (1) a closer liaison, a greater frequency of conference between technical laboratorian and clinician and (2) a joint control by synthesist and tester of the procedure and personnel used in testing. We have seen enough examples of the serious errors to which a purely laboratory outlook may lead to believe that it is essential that each new drug before it is put to use in man be criticized by a clinician thoroughly familiar with the pathologic conditions in which it is to be used and the pharmacology and therapeutics of the special field of medicine involved. A knowledge of research or practical pharmacology in general is not necessarily equivalent to special knowledge of the course and treatment of a widely disseminated and multiform disease. With such improved contact laboratorians will cease for example to demand the clinical testing of nonspirillicidal drugs on unhospitalized patients with acute infectious syphilis and to distribute through their manufacturing concerns without previous conference preparations of which certain types of reactivity and cumulative effect could have been predicted for man from the start, regardless of the tolerance and response of rabbits. In the choice of testing organizations and cooperators too, the laboratorian, no less than the technical organization as a whole, needs the advice of one familiar with the clinical field. Some men, some clinics and some types of clinical material are suited to a drug-testing undertaking and some are not, as will presently appear.

The establishment by technical organizations of research nuclei in clinics the material and direction of which render them suitable for drug-testing projects is an advance over any form of casual affiliation based on circumstance. It recognizes in the first place the fact that adequate study of the clinical behavior of drugs demands brains and that they are not to be had for nothing, or for a sop of free supplies. The house which relies on hand-outs too often gets hand-outs of impressionistic and casual observation in return. The subsidizing of a worker permits stable technical performance and, if the grant is adequate, proper follow-up and sustained constructive thinking which may have important practical results. The practice is now a well established one in a number of basic industries, and we know of no evidence that scientific institutions have been rendered venal, biased or corrupt by such properly guarded contacts. There will be, as we have noted, at the present stage of development of drug-testing procedure a certain amount of die-hard criticism of those who have presumably sold themselves to Mammon in the person of a fellowship-endowing technical organization, but such criticism must apply with at least equal force to those who accept drugs otherwise than as bought on the open market. In the end, the only test of such forms of organization of the drug-testing

problem must lie in the honesty and worth of their scientific output, the good name of those who enter into such arrangements and the form of agreement to which both parties to such an arrangement subscribe and adhere. Such agreements should not be personal but rather institutional, and only by avoiding every suggestion of personal advantage and remuneration and by the frankest publication of set-up can parties entering into them hope to draw the sting of jealousies and distrusts inevitable in rivalry among human beings and in the evolutionary history of such undertakings.

The establishment of a fellowship and the acceptance of a grant, large or small, should be a matter of contractual arrangement in writing, defining the following matters:

1. The purpose, the amount and duration of the grant and the selection of the incumbent.

2. The terms on which facilities are to be provided, used or exchanged.

3. The reservation of absolute title by the clinical or scientific organization to the facts and interpretations derived from the investigation.

4. The absolute control of release and publication of its material by the clinical organization. Misuse of informal quotation and propaganda must be specifically provided against.

5. The right of the founder of the fellowship to (*a*) a voice in the problems chosen and (*b*) periodic informal information as to the course of the investigation.

6. Assurance of justified priority in publication and reservation of a voice by the clinical authority in the choice and activity of collaborators and of collateral lines of investigation.

7. The handling of funds through a disinterested group agency of unimpeachable ethical standing. While this can be waived in the case of small grants, either of money or of materials, it is a proper safeguard to all concerned in larger undertakings, especially if they include a full time salaried incumbent.

8. The conduct of all communication and the direction of research jointly by the heads of the clinical and the manufacturing laboratory organizations, and not by associates, subordinates or the holders of fellowships themselves. This filtering of all exchanges and results through the chiefs provides the nearest approach to a fool-proof control of policy available. A head of a clinical or technical laboratory who will not give this measure of personal supervision to scientific-technical research associations can expect to suffer the embarrassments ensuing on "grapevine telegraphy," whisper campaigning and evasion of respon-

sibility for unauthorized statements which spring up in spite of all the good will in the world under delegated responsibility.

METHODS AND PROBLEMS OF THE CLINICAL INVESTIGATOR OF ANTISYPHILITIC DRUGS

After the clinician has successfully dealt with the problems of sampling and sales organization approach and has achieved a successful liaison with a serious and competent scientist on the manufacturing side, by grant, exchange of facilities or establishment of a research fellowship of general scope, he must proceed to the internal organization of testing procedure. Our experience points to the several considerations as essential in our field.

Syphilis is a disease of great complexity and chronicity. Experimental study dealing with it calls on the laboratory side for what amounts to the maintenance of an animal hospital over a period of years, in which the simplest evaluations are matters of months at the very least. This is especially true of therapeutic evaluations. But if the evaluation of a result in animals takes months, in man, who cannot be reduced to organ hash at will, it takes years. The clinical investigator must therefore (1) subdivide his reports chronologically into periods; (2) accept for testing only drugs for which he has the proper clinical material in sufficient amount; (3) maintain a stable evaluating mechanism, including a laboratory equipped for controlled serologic and dark field examinations and clinical assistants with not less than two years' experience with the disease; (4) have available a follow-up mechanism which will secure continuity of treatment and returns for reexamination in a large proportion of cases over a long period of time, and (5) develop a treatment organization which can be relied on for constant performance in the technic of injection, a normal incidence of unavoidable reaction to ordinary drugs and the development of special facility and accuracy in detecting both therapeutic response and reaction to the new drug. Deficiencies in any of these particulars may reduce the results of any test procedure to mere impressionistic opinion, no matter how distinguished the evaluator.

After the synthesist or manufacturer has produced evidence in conference of the low toxicity and high therapeutic index of his product in normal and syphilitic rabbits, the two primary questions confronting the clinician, to our way of thinking (in which we disagree with Snodgrass [5]) are as follows:

1. How spirillicidal is the drug in man?
2. Are there harmful by-effects not disclosed by the study of animals?

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5. Snodgrass, W. R.: The Methods to Be Employed in the Investigation of New Substances Designed for the Treatment of Syphilis, Brit. J. Dermat. **98**: 11-20 (Jan.) 1936.

It is vital to establish the spirillicidal action of the drug in man at the outset because, regardless of every precaution, if the drug is offered for use in antisyphilitic treatment it will be used in cases of early stages of the disease. Failure to control infectiousness, in the present state of general comprehension of antisyphilitic treatment in this country at least, is a deficiency in public health control of the first magnitude and must be reported at once and in unmistakable terms. Tryparsamide, for example, must not be used for early syphilis even though there is involvement of the nervous system; the slight difference between the spirillicidal control exercised by bismuth falls sufficiently short of that provided by the arsphenamines to be blamed for widespread extension of the disease in France; an intravenous mercurial the efficacy of which is stated by a laboratorian to be equal to that of the arsphenamines proves to have almost negligible spirillicidal action on acute lesions in man.[6] Every form of antisyphilitic medication must, then, be tested first as a spirillicide in man. Its subsequent action, while critically important, is secondary. If drugs known to have low immediate sterilizing power are to be investigated, patients with early syphilis receiving those drugs must be hospitalized.

It is obvious, then, that experience in searching for spirochetes and full control of patients to the extent of hospitalization are primary requisites in this field not possessed by the sample-using type of practicing physician. It should be emphasized that the healing of a lesion, so generally revered by the inexperienced as the test of the effectiveness of a drug, is not synonymous with surface sterilization and may be totally misleading as a guide to public health efficiency.

The determination of toxicity for man (i. e., reaction incidence), the second duty of the clinical investigator, involves the following considerations: A distinction must be drawn between (*a*) immediate and ultimate and (*b*) major, or serious, and minor, or incommoding, reactions. It must be realized that incommoding reactions such as local pain or reaction at the site of treatment may be serious from the standpoint of public health, and actually render an otherwise good drug useless because patients and physicians will not persist in its use and the former may abandon any kind of treatment in consequence. Serious reactions may appear with the first few injections given in a test series and then disappear or prove on continued use of the drug to be a minor problem. The relation of dosage to serious reaction must be determined early, for a good reaction record may be the product of a dosage which

6. Ingraham, N. R.: The Organic Mercurials and the Mercury Therapy of Syphilis, with Special Reference to Hydramilon, Pennsylvania M. J., to be published.

is therapeutically inadequate immediately or ultimately. For the proper evaluation of minor reactions, average outpatient clinics with inefficient follow-up service and technically proficient but medically ignorant or lethargic treatment staffs may be entirely incompetent. It is surprising how few complaints patients make spontaneously. They simply disappear. Special effort and attention may therefore be needed for such interpretations, and a single stable experienced head to the investigation becomes essential. Among important reaction determinants often lost sight of in routine test procedure we have noted faulty intramuscular technic under different operators, inadequate or variable postinjection massage and lot variation, which may lead every single injection of a given batch to give rise to a violent reaction not duplicated by ensuing lots and due possibly to a physical dispersion state or impurities since no toxicologic differences are apparent. In intravenous procedure variations in rate of injection are often critical (vide the contrast between mapharsen and neoarsphenamine), and a hurried or driven operator may distort the entire picture of a drug's reaction-producing qualities. Persistence in treatment after inconspicuous signs of intolerance have developed but not been noted (e. g., purpura, itching) may make a drug appear dangerous because of entirely avoidable catastrophes. On the other hand, such expert use as can rarely be duplicated in ordinary practice may give a false impression of the showing the drug will make in the hands of physicians at large, among whom lower standards are apt to prevail. A testing organization should, we believe, conform to the type of procedure for reaction control which we have previously described,[2] including physical inspection, the use of the reaction questionnaire, the weekly examination of urine, complete blood counts on markedly reactive patients as well as on those with anemia or dermatitis and tests of the function of the liver in selected cases. Patch tests may be of some value, especially when the occurrence of mild dermatitis may make the cautious operator withhold further arsenical treatment. The evaluation of the patch test by one of us (H. B.)[7] has suggested that it is not specific enough to be implicitly relied on as an indicator of sensitization to arsphenamine. It has failed as a reliable means of detecting the specific allergic factor in arsenical cutaneous reactions other than typical arsphenamine dermatitis occurring during treatment with arsphenamine. Furthermore, indiscriminate use of the test may not be entirely harmless, since it may cause an exacerbation of a subsiding dermatitis and repeated application of the test may apparently induce cutaneous sensitization to the arsphenamine in question.

7. Beerman, H.: The Patch Test in the Determination of Arsphenamine Sensitization, Pennsylvania M. J. **39**:690-695 (June) 1936.

Next in importance after the determination of spirillicidal and reaction-producing effects, we rate the following considerations in order of importance:

3. Herxheimer effect or therapeutic shock. This is more important inferentially in cases of late than in those of early syphilis but is more safely interpreted and studied in the former.

4. Healing of lesions (primary, secondary and late benign). This is classified under injections, dosage and days.

5. Symptomatic response with respect to particular structural units. Always of special interest are the highly refractory symptom complexes of tabetic pains and gastric crises, primary atrophy of the optic nerve and deafness.

6. General constitutional (tonic or depressant) effect, including weight, well-being, outlook and working capacity.

7. Effect on the serologic reaction of the blood. For the ideal plotting of the curves of (*a*) rate of decline to negative reaction, including premature (low resistance), normal and delayed reactions, (*b*) positive serologic reactions developing from the late seronegative primary stage and (*c*) weakly positive reactions as warnings of relapse, a weekly serologic test by a Wassermann (Kolmer) and a precipitation procedure is desirable. Persistently positive serologic reactions should also be studied by a double test procedure.

8. Observation for clinical relapse, especially mucocutaneous involvement, and for evidence of progression.

9. Reaction and response of the spinal fluid. This presupposes a smoothly running technic of obtaining fluid and prompt examination, applied in all cases of early syphilis and in reexaminations, as well as in evaluation of latent and other types of the disease early in the course of their treatment. Reports on serologic and clinical observations not controlled by examination of the spinal fluid lose much of their ultimate value.

10. Evidence of therapeutic paradox (injury by too rapid healing).

11. Evidence of significant organic damage from treatment (aplastic anemia, nephrosis, hepatic injury, ocular disturbance).

12. Special study of the effect of the drug in the prevention and treatment of cardiovascular conditions and neurosyphilis, in pregnancy and in interstitial keratitis.

Controls required for study of an arsenical drug in particular—but for study of drugs in general—and too often overlooked in clinical reports include the following considerations:

An effort should be made to ascertain the results obtained by use of the drug alone in a number of cases and under hospital or other control

that will fully protect both the patient and the public. Since the statistics reported by the Cooperative Clinical Group [8] indicate that a patient may be allowed to go on to secondary syphilis without significant loss of chance for recovery, provided he is subsequently treated by a continuous system, it is, we believe, permissible to test the response to a drug in seronegative primary stages as well as in early stages of secondary syphilis. But it is not allowable in our estimation, at this stage of knowledge, to try a drug of known or suspected low spirillicidal value in treating patients with early syphilis in an outpatient service for example or to jeopardize a human being's chance of cure by treating him for early syphilis over a prolonged period with a new drug used alone when there is the slightest reason to suppose that his resistance is being impaired or endangered, his infectiousness insufficiently controlled or the prospect of relapse or injury to a special system neglected or increased. Man, after all, is not an experimental animal. For this reason the tester should from the start employ parallel series of the new drug used alone and combined treatment (arsenical and heavy metal) and should have available experience with a standard drug (neoarsphenamine or arsphenamine) against which to check the tested drug at frequent intervals to see whether its performance week by week justifies its continuance or not. Experience is needed here, and the weighing of quick but evanescent effects against slower but more lasting ones or the defining of a special and highly limited field of usefulness is no affair for the unsupported and inexperienced sampler. Bismuth might easily have lost its place in the therapy of syphilis if it had been first examined by an overbalanced spirillicide enthusiast or by a serologist who overemphasized its relatively slower effect on the serologic reactions of the blood.

If the test of the drug is to be made as a basis of comparison with the work or observations of other examiners and reporters, the utmost care must be observed in reduplicating the technic of the person whose results are to be discussed or criticized. Notable examples in the literature of exasperatingly uninterpretable comparisons and even ill tempered aspersions arising from oversight in this particular aspect of the procedure can be cited. One of the oldest in the field of investigation of

8. Clark, T.; Parran, T., Jr.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Stokes, J. H., and Wile, U. J.: Cooperative Clinical Studies in the Treatment of Syphilis: I. Introduction, Ven. Dis. Inform. **13**:135-139 (April) 1932. Stokes, J. H.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Clark, T.; Parran, T., Jr., and Usilton, L. J.: Cooperative Clinical Studies in the Treatment of Syphilis: Early Syphilis, ibid. **13**:165-182 (May); 207-231 (June); 253-293 (July) 1932. Stokes, J. H.; Usilton, L. J.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Parran, T., and McMullen, J.: What Treatment in Early Syphilis Accomplishes, Am. J. M. Sc. **188**:660-684 (Nov.) 1934.

the arsenicals—the check test made on J. B. Murphy's [9] reported results with sodium cacodylate given intramuscularly—has been cited elsewhere.[2] Precisely as in the comparison of the specificity and sensitivity of serologic tests of the blood, in which an individual serologist's slight technical variations lead to wide disparities in outcome, so in drug testing the strictest uniformity of conditions must be preserved by observers seeking to compare results and by a single observer using parallel series for comparative purposes within his own service. For example, in our work with bismuth arsphenamine sulfonate, in which we used two services, the difference in significant incidence of local reaction conditioned by the better placement of the needle and more thorough massage in the one as compared with the other was clearly apparent.

In the handling of a drug, if possible by an organized team headed by a responsible and experienced investigator, the first essential of painstaking work made possible by such an arrangement is the keeping of adequate protocols, especially of records of reactions. Looseness in matters of record is a notorious fault of clinical investigation and may reduce what might be adequately supported and well digested experience to mere impression and guesswork. The correction of remediable technical causes of reaction or the adaptation of technic to the peculiarities of the drug, so as to iron out an initial excessive reactivity, depends almost entirely on the combination of adequate records, team-work and experienced directorship. Moreover, only by such coordination can the chemist and the manufacturer be given sufficiently definite information as to the extent and probable cause of a given trouble to make possible attempts by the manufacturer to improve the product and remedy the difficulty.

A fourth element of control concerns the already mentioned personal equation factors in the evaluation of a drug. Foremost of all such considerations must be the temperamental type, reactions and prejudices of the clinical investigator. Trite though it may seem to remark on the fact that he is human, it is impossible to work in this field without accepting and to some extent discounting the fact. Clinicians have a tendency to indulge in autistic, individualistic and personal reactions toward problems, as distinguished from the more abstract and detached thought processes which are the products of the "scientific" temperament and training. The manifestations of this bent vary from personal likes and dislikes for drugs, persons and manufacturing concerns to personal pride, jealousy, wishful thinking and participative bias, covering almost any aspect of the clinical testing of a

9. Murphy, J. B.: The Arsenical Treatment of Syphilis, J. A. M. A. **55:** 1113-1115 (Sept. 24) 1910.

drug. The swing of an individual tester or a testing group in one direction or another among these possibilities is one of the strongest reasons for multiplying the number of otherwise competent investigators conducting the clinical evaluation of a product. We have come to recognize it as inevitable that we shall feel a certain measure of competitive partisanship and rivalry, that we shall have difficulty in seeing the good in the work of one who, however justifiably, has once turned down, rejected, criticized or minimized us and that we shall inevitably have to struggle with a certain prejudice in favor of our brain child and a certain amount of wishful thinking with regard to its merits and future. In our experience the reduction of bias in these directions consists (1) in the conscientious effort to recognize that these elements of bias exist; (2) in systematic rejection of snap judgment and early impressions with regard to the clinical behavior of a drug initially properly studied and credentialed in the laboratory; (3) in the scrupulous return to adequately kept records for each point in evaluation, and (4) in a full exposé of the entire set-up in the published report with an invitation to the most searching criticism. Regardless of every precaution which can be thrown about the subjective and personal equational elements in a clinical study, two things are practically inevitable: The first investigator's report will be too optimistic, and time will inevitably lead to a certain degree of disillusionment. *"The* new drug" will settle down to "*a* new drug," and "a *new drug*" will ultimately become "a drug" in the case of 999 of 1,000 synthetics subjected to clinical test. As Barrio de Medina[10] remarked, a new preparation of arsphenamine becomes simply "one more brand of arsphenamine," with a certainty that can only be compensated by the establishment of a definite, even though circumscribed, field of usefulness for each new and acceptable preparation.

This summary of the element of personal equation leads to the conclusion that time—and a long time at that—is essential to the dispassionate, balanced evaluation of a chemotherapeutic synthetic, at least in the field of syphilis, and that the tendency to overexpand and overestimate the field of usefulness of a new drug must be resisted by every critical faculty.

The time periods into which the study of an arsphenamine seems to us best to resolve itself are determined by the following factors:

1. A determination of surface spirillicidal action and healing power which can be arrived at in, let us say, from sixty to ninety days.

10. Barrio de Medina, J.: Silver Arsphenamine in the Treatment of Syphilis, Arch. Dermat. & Syph. **5**:321-324 (March) 1922.

2. The power of the drug to reverse the serologic reaction, which will require for preliminary interpretation, say, twenty weeks and for ultimate interpretation in early syphilis from eighteen months to two years.

3. The effect of the drug in the prevention of relapse, of the acute infectious type and consisting of involvement of special structures such as the liver, the bones and the nervous system, which will require from two to four years but can have a preliminary interpretation at the end of one year.

4. The effect of the drug on resistant syphilitic manifestations such as a positive Wassermann reaction and necroses of bone, especially of the nose and skull, the action on pain and the effect on gastric crises, persistent lightning pains, asymptomatic neurosyphilis of the "preparetic" type and cardiovascular syphilis. None of these observations will require less than two years, and in all probability from three to five years of study will be necessary.

5. The ultimate curative action of the drug in man, the preliminary evaluation of which can be accomplished within five years but which can be carried on indefinitely through the first and second decades.

In contrast with this chronological and scientific alinement of the investigation, the points on which the majority of physicians interested in syphilis first desire information, given somewhat in the order in which they desire it, are as follows:

1. Will the drug injure or alienate my patient by either minor or serious reaction?

2. Is its administration so elaborate, so complicated or so hedged about with precautions as to constitute an inconvenience in the office?

3. Will it cause rapid healing?

4. Will it quickly relieve symptoms, especially pain?

5. What will it do for patients with a persistently positive Wassermann reaction?

It is, of course, along lines such as these that sales campaigns and advertising will tend to be drawn. The questions which concern the expert and the public health authorities have as yet relatively little influence on the popularization of a new synthetic drug in the treatment of syphilis. These have been largely reviewed in the discussion on the examination of a new drug. One of the most important of these questions today is: Can the new drug be fitted into the continuous and intermittent systems of treatment for early syphilis adopted by the Cooperative Clinical Group and the League of Nations without loss of the now established advantages afforded by these systems in the control of early syphilis with arsphenamine, neoarsphenamine and heavy metal

preparations (bismuth)? At the present time it is, we think, a serious criticism of any drug which is expected to occupy a place in the modern treatment of syphilis that it should be inadequate in controlling infectiousness or that it should yield "curative" serologic and symptomatic results in any way inferior to those now established for the treatment of early syphilis with the standard arsenicals. Granted, however, that a new synthetic drug definitely falls short or exhibits marked diversity of results among investigators on these critically important issues, is the preparation to be regarded as useless? By no means. The very slowness of effect in spirillicidal action and healing which a drug may exhibit in the first six months of its use may prove a substantial asset in the treatment of some phases of late syphilis, particularly of syphilis of the cardiovascular and hepatic structures. A definite superiority in reducing persistently positive serologic reactions of the blood to negative, especially in latent syphilis, of which there is an enormous amount now in existence, would fully justify the introduction of a new synthetic to the profession. A drug with a peculiarly rapid and intense spirillicidal action capable of producing surface sterilization of relapse lesions in treatment-resistant syphilis unresponsive to other arsphenamines would similarly have an important place in modern antisyphilitic therapy, even though the action of the drug used alone was inadequate with respect to ultimate power to reverse the serologic reaction and ultimate curative results. A third type of drug with a special field of usefulness would be one which, though it possessed delayed spirillicidal effect, could be substituted for a standard arsenical group to which serious intolerance had developed. When such distinctive fields of usefulness or evident limitations appear in the clinical examination of a drug, it becomes the duty of the manufacturing concern to exercise particular restraint on its sales organization and to be particularly conservative and close mouthed in its claims for the usefulness of the preparation, and it becomes the duty of the clinical tester to see whether, by combining the new preparation with other drugs and by varying the technic of administration, the special advantage can be conserved and the deficiencies lessened. This again is no undertaking for inexperienced testers and uncontrolled sample testing.

It must be apparent that in attempting to meet all the possible requirements for adequate testing of a drug the clinical investigator, unless he is at the head of a positively utopian aggregate of patients and a superlative organization, will be severely taxed to provide the necessary volume of material of various types, on the one hand, and to exercise an adequate control over his organization, on the other. If the synthesist's brain is fertile he will swamp his clinical cooperators with requests for evaluation, and if his output of energy and his drive

are large he will promptly turn sometimes to uncontrolled and unreliable cooperation for his lesser clinical tests. The pressure for a "showing" on a drug from the commercial side and the abounding and sometimes pernicious energy of a sales organization will accentuate and take advantage of the personal equation factors of wishful thinking, brain-childism and rivalry involved in the project as a human undertaking. Against these elements of cross-pressure and strain on sound evaluation we suggest a consideration of the following nationally applicable scheme of reorganization of the drug-testing field. We do so, however, with a certain, though probably not adequate, awareness of the shortcomings of organization as regards methodology and impersonalization in this as well as in other situations.

A SUGGESTED PLAN

Proceeding on the theory that the adequate evaluation of the therapeutic worth of a drug should be divorced as far as possible from personal equational and commercial influences and considerations, that it requires the kind of knowledge possessed by a chemical and biologic experimental laboratory, that it demands detailed and expert clinical knowledge of a disease, that it has highly important aspects from the standpoint of, and relationships to, public health; that it involves great expense and much time in evaluation, and that the volume of work awaiting consideration is probably far in excess of the organized and controlled clinical material as yet available for its evaluation, it seems that the following plan offers the nucleus of a unified, well balanced and effective program. Items of this program have demonstrated a certain amount of economy, practicability and soundness in connection with other basic industries, such as steel refractories, metallurgy and mining. The precedent of governmental interest in private technical evaluation problems, while still none too well defined, has, we believe, been recognized in some of its essential features in the National Institute of Health, the various divisions of the Department of Agriculture, the United States Bureau of Standards and the Bureau of Mines. In order to avoid the initial difficulties of paternalistic and patriarchal intervention by the government in private enterprise and the expenditure of public money on research which may result in private profit, we have proposed the internal organization of the chemical synthetic and biologic testing aspects of the problem by the pharmaceutic industry itself, subject to governmental control and check.

The first step in execution of this plan is the calling and, if preliminary arrangements are successful, the voluntary institutionalization of a round table conference of drug manufacturers and clinical (syphilologic) experts, including representatives of the Council on Pharmacy

and Chemistry of the American Medical Association—the first representing the technical side and the last two the medically expert side and the human test material involved. In order to introduce into this set-up the important elements of impersonalization, of test authority already legally recognized and of public health control and interest, this round table conference should be under the chairmanship of the division of venereal diseases of the United States Public Health Service.

If the preliminary round table conferences have a satisfactory tone and both the technical and the clinical side evince a cooperative spirit, formulation of standards of clinical procedure for the clinical group and development of a cooperative institute for the testing out and joint handling of certain technical problems in manufacture may be undertaken. In a small way and under responsible direction acceptable to the round table group, such problems as the storage and rate of elimination of drugs may be undertaken by a central analytic set-up, and a central agency for the testing of toxicity and spirillicidal effectiveness, working alone or in cooperation with the National Institute of Health, can be developed. Individual pharmaceutic concerns could next well afford to ponder the savings made possible by synthesis of certain basic products in a central technical plant, and from this point on the development of research possibilities, fostered by the industry as a whole rather than by competing rival units, might reasonably be conceived. Some of the preeminence of German synthetic chemistry in the first two decades of this century was fostered by such a type of organization. It is essential, however, to emphasize that disinterested public health authority and expert clinical knowledge of disease must be represented in the completely rounded organization, together with expert biologic and pharmacologic knowledge. A union of the public health, the academic and clinical and the technical manufacturing interest in a plan of this sort would do away with much of the undesirable practice discussed in the earlier part of this paper.

II. THE DRUG TRIARSEN AND ITS CHEMOTHERAPEUTIC AND CLINICAL INVESTIGATION

THE INVESTIGATIVE SET-UP; THE ABBOTT FELLOWSHIP

The investigation of bismuth arsphenamine sulfonate (bismarsen) undertaken in the department of dermatology and syphilology of the School of Medicine and the Hospital of the University of Pennsylvania from 1925 to 1930 illustrated both the good and the bad qualities of the casual type of liaison between a chemist engaged in the study of arsphenamine and his organization and an academic clinical group. When the study of this drug had passed its fifth year it was agreed between the responsible heads of the organizations concerned that a

fellowship supported by an annual grant from the pharmaceutic manufacturing concern within the clinical organization would serve the best interests of a further drug-testing undertaking. The Abbott Fellowship in Chemotherapeutic Research was therefore proposed, and a contractual agreement, practically identical with that previously described, was drawn up between the Abbott Laboratories and the University of Pennsylvania. Under the terms of this grant there is no formal or informal connection of any person in the department of dermatology and syphilology with the Abbott Laboratories, and vice versa. As the head of the department of dermatology and syphilology was a member of the Cooperative Clinical Group associated with the United States Public Health Service, the contractual agreement was submitted to this group at one of its regular sessions and its consent obtained for the clinic of dermatology and syphilology to receive the representative of the Abbott fellowship and at the same time to continue its association with the Cooperative Clinical Group. At each step in the arrangement experienced members of the university and medical school organization were consulted, and every possibility that could be foreseen was provided for. The fellowship has had one incumbent (H. B.) throughout the four years of its life and has illustrated in its operation a number of the advantages of this form of organization. Not only have three chemical substances been subjected to clinical test, but the representative of the Abbott fellowship has been generously supported in an extended and expensive experimental study on animals of treatment-resistant syphilis which constituted a purely scientific research.[11] There have been a number of interchanges between the laboratory and clinical directors looking toward the improvement of chemotherapeutic technic and the better utilization of clinical testing material.

EFFECTS OF THE DRUG TRIARSEN

The new arsenical under consideration, synthesized by Dr. G. W. Raiziss, of the Dermatological Research Laboratories, is the trisodium salt of 3,3′ diamino 4,4′ dihydroxyarsenobenzene N,N′ dimethylene sulfonic acid. It has been provisionally designated "triarsen." It is a water-soluble yellow powder and contains not less than 19 per cent of arsenic. Its aqueous solutions are lemon yellow and neutral or slightly alkaline. Its toxicity record and therapeutic activity in animals indicate that it is a rather potent but safe drug. Its chemotherapeutic index in animals is 18, as compared with from 6 to 10 for the similarly computed indexes of various neoarsphenamines (these indexes are the ratio of the maximum tolerated dose

11. Beerman, H.: The Problem of Treatment-Resistant Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:165-206 (March); 296-334 (May) 1936.

in rats to the minimum therapeutic dose in rabbits [550/30 for triarsen, as compared to from 240 to 400/40 for neoarsphenamine]). Triarsen is given intravenously in a concentration of 0.1 Gm. to 2 cc. of distilled water. Originally physiologic solution of sodium chloride was used as the solvent. Because on the basis of tests on animals the drug's record as a spirillicide and its chemotherapeutic index indicated that it safely and effectively controlled infectiousness it was placed on trial in the outpatient department of the syphilis clinic of the Hospital of the University of Pennsylvania in March 1932, and the controls and the procedure described in part I were employed.

At the outset one group of patients was treated with the drug alone, and later another group was treated with the drug plus bismuth. We had available for comparative purposes the incidence of reaction, data on clinical and serologic response and the standard expectation of relapse afforded by the statistics furnished by the Cooperative Clinical Group and the League of Nations,[12] the figures of Cannon and his co-workers[13] for arsphenamine, neoarsphenamine and silver arsphenamine and the recently published data of Foerster and his co-workers[14] and of Kulchar and Barnett[15] on mapharsen.[16] We also utilized our experience with sulfarsphenamine (Stokes and Behn) and with bismarsen (Stokes, Chambers, Miller and Beerman) as well as the published experience of Lévy[17] on the expected spirillicidal power of both neoarsphenamine and bismuth.

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12. Martenstein, H.: Syphilis Treatment Enquiry in Five Countries, Quart. Bull. Health Organ., League of Nations **4**:129-246 (March) 1935. Martenstein, H., and Gougerot, H.: Ann. d. mal. vén. **30**:481-493 (July) 1935.

13. (*a*) Cannon, A. B.: Value of Silver Arsphenamine in the Treatment of Early Syphilis, J. A. M. A. **102**:268-273 (Jan. 27) 1934. (*b*) Cannon, A. B., and Karelitz, Marie B.: The Comparative Value of the Arsphenamines in the Treatment of Early Syphilis, J. A. M. A. **97**:1523-1530 (Nov. 21) 1931.

14. Foerster, O. H.; McIntosh, R. L.; Wieder, L. M.; Foerster, H. R., and Cooper, G. A.: Mapharsen in the Treatment of Syphilis: A Preliminary Report, Arch. Dermat. & Syph. **32**:868-889 (Dec.) 1935.

15. Kulchar, G. V., and Barnett, C. W.: Mapharsen in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:482-486 (Sept.) 1936.

16. The data of Gruhzit and his co-workers (Gruhzit, O. M.; Dixon, R. S.; McAlonan, W. T.; Sherman, W. L.; Merriman, K. S.; Sewell, G.; Arnold, E.; Dowling, P. C.; Pierson, M.; Chambers, E. R., and Lauppe, F.: Mapharsen in Mass Treatment of Syphilis in a Clinic for Venereal Diseases, Arch. Dermat. & Syph. **34**:432 [Sept.] 1936) on mapharsen were not available to use until the time this paper was submitted for publication, and are consequently only partially utilized here.

17. Lévy, G.: Recherches sur l'action tréponémicide comparée des divers sels bismuthiques et des arsénobenzenes, Bull. Soc. franç. de dermat. et syph. **37**:877-879 (June) 1930.

The new drug triarsen was administered to a total of 126 male and 63 female patients over a period of four years and three and a half months, a total of 3,009 injections being given. The number of injections administered to each patient ranged from 1 to 53 (1 case). Sixty-one patients received 20 or more injections of the drug. In accordance with the scheme of investigation outlined, our principal effort has been directed toward the determination of the effect of the drug in early syphilis. Fifty-eight of the patients treated presented primary lesions, 22 of them having negative serologic reactions. One hundred and eighteen patients presented secondary cutaneous manifestations, and 10 had latent syphilis. No attempt has been made thus far to evaluate the efficacy of the drug for other lesions and stages of the disease.

At the outset the new drug was used alone for as many as 22 injections. Patients who received sufficient injections to afford data on the points studied were given triarsen and bismuth therapy simultaneously. All treatment was continuous; there were no rest periods; and patients who lapsed in treatment were reexamined whenever possible.

The first consideration was that of the spirillicidal action of the drug. On this point our present and previous experience has impressed us with the importance of a prolonged search by technically adequate personnel with adequate equipment for detecting Spirochaeta pallida. The majority of the organisms disappear quickly, but an occasional one can be observed after careful search. The organisms disappeared from superficial lesions in from less than twenty-four to ninety-six hours, a period corresponding almost exactly with the expectancy for neoarsphenamine on the basis both of observations in our own service and of reports in the literature. The initial dose of 0.3 Gm. was apparently as effective in bringing about the disappearance of organisms as was the maximum dose of 0.6 Gm., an observation confirming some current conceptions in the case of neoarsphenamine. Foerster and his co-workers found that mapharsen caused spirochetes to disappear on the average within twenty-four hours, but the report of Gruhzit and his colleagues allows for periods up to three days.

Reactions to the Drug.—While the patients were treated in an outpatient department, practically all of them were personally seen and questioned by one of us (H. B.) on each visit, so that the figures for reactions include many of the minor type which would escape notice in a less searching inquiry. Eighty of the 189 patients treated sustained 1 or more reactions. Six patients exhibited intolerance for triarsen, and the drug had to be discontinued. One who exhibited intolerance for neoarsphenamine tolerated triarsen, and 6 who exhibited intolerance for triarsen received neoarsphenamine without reaction. One who did not tolerate triarsen received bismuth arsphenamine sulfonate with-

out reaction. Table 1 presents the comparison of the new drug with arsphenamine, neoarsphenamine and mapharsen on the basis of the proportion of reactions of each type to the total number of injections.

It is apparent that the incidence of minor incommoding reactions to triarsen tends to be about as high as that of reactions to neoarsphenamine. From the standpoint of securing attendance at the clinic, therefore, and consequently of the conservation of the public health interest in the treatment of syphilis, triarsen is about the equal of neoarsphenamine. In comparison with mapharsen, triarsen has the advantage, at least so far as can be gathered from our available figures. We feel, however,

TABLE 1.—*Comparison of Types of Reactions to Arsphenamine, Neoarsphenamine, Triarsen and Mapharsen* *

	Percentage of Total Number of Injections					
	Mayo Clinic 1923		Kulchar and Barnett		Kulchar and Barnett	
Reaction	Arsphenamine	Neoarsphenamine	Neoarsphenamine	Triarsen	Mapharsen	Foerster et al.
Nausea and vomiting	19.5	4.0	4.8	3.0	10.4	3.4
Headache	7.9	2.0	4.1	0.3	7.1	0.6
Diarrhea	2.5	0.5	0.6	...	4.3	0.9
Fever	1.5	0.4	...	0.5†	...	...
Nitritoid crisis	1.2	...	2.1 ?	0.6	1.1 ?	0.0
Technical complications (arm)	1.2	0.1	0.0	0.1	0.9 venous thrombosis	+ venous sclerosis
Chills	1.1	0.4	0.7	0.5†	1.8	...
Abdominal pain	0.8	0.4	1.1	0.1	1.2	0.1
Backache	0.7	0.1	...	...	...	...
Flush	0.4	0.2	...	...	...	...
Pains in legs	0.2	0.1	...	...	...	...
Dizziness	0.3	0.1	1.9	...	2.5	0.2
Cutaneous (mild)	0.1	0.0	2.3‡	0.5‡	1.4‡	0.6
Miscellaneous	0.5	0.0	...	0.03§	...	0.4‖

* Adapted from Stokes,[2] p. 423.
† Chills and/or fever.
‡ Reaction included exanthem.
§ Questionable arsenical hepatitis.
‖ Lacrimation and salivation.

that the published figures for the reactions to neoarsphenamine are somewhat higher than those we have encountered in our recent practice in the clinic. A sample of the data from the records from our treatment room shows that during the period of observation the number of reactions to neoarsphenamine "on the table" was several times less than that of reactions to triarsen. A longer period of observation probably tends to make the ratios more nearly alike. The proportion of nitritoid reactions to triarsen is not alarming. A certain number of the reactions are due to the fact that one of our colleagues (D. M. Pillsbury) used several of the patients who experienced one nitritoid reaction as material in a study to test the amount of drug necessary to induce such a reaction in such a patient. The revised results were not different from those obtained with neoarsphenamine.

On cutaneous reactions special comment is necessary. In 2 cases dermatitis (in 1 case severe and in 1 mild) occurred early in the use of triarsen. We were able to resist the strong impulse to discard the drug after these occurrences the more readily because there seemed to be some reason for suspecting that routine preliminary patch testing which we had used in the effort to identify a basic preadministration sensitiveness to the drug might, as we thought at the time, have resulted in a definite sensitization of the patients to triarsen. Whether or not this explanation was sound, no further cases of dermatitis occurred after patch testing was stopped until approximately 1,500 injections had been given. The third cutaneous reaction was a typical exfoliative dermatitis. It occurred after the fifth injection of an arsenical, and while

TABLE 2.—*Comparison of Healing Effect of Triarsen with That of Other Antisyphilitic Drugs*

Drug	Grams	Injections	Days
Average Time and Amount of Treatment Required for Healing of Primary Lesions *			
Arsphenamine	1.05	2.6	9.3
Neoarsphenamine	2.96	4.8	21.3
Silver arsphenamine	1.15	5.0	20.9
Triarsen	1.63	3.1	17.6
Triarsen and bismuth subsalicylate	1.05	2.6	14.4
Mapharsen (seropositive)	0.2775	4.5	15.25
Mapharsen (seronegative)	0.333	5.5	19.33
Average Time and Amount of Treatment Required for Healing of Secondary Lesions			
Arsphenamine	1.43	3.98	17.5
Neoarsphenamine	3.30	6.18	23.7
Silver arsphenamine	0.765	4.02	16.08
Triarsen	1.22	2.70	13.80
Triarsen and bismuth subsalicylate	0.98	2.50	13.80
Mapharsen	0.1734	3.30	12.0

* Cannon [13a]; Foerster et al.[14]

the patient recovered completely, the reaction was fairly severe. The total number of cases of dermatitis to date is therefore 4, or 1 for each 750 injections, which is undoubtedly high.

No local reactions occurred which destroyed the usefulness of the vein employed (there was no venous thrombosis). The drug does not differ from neoarsphenamine, however, in its local irritant properties when extravasation occurs.

The tendency of triarsen to produce reactions, then, is about equal to, or slightly higher than, that of neoarsphenamine. In this particular characteristic it tends more to approach arsphenamine. It may prove to share with sulfarsphenamine a tendency to produce cutaneous reactions. It does not, however, at least in an experience with 3,000 injections, have a deleterious influence on the hematopoietic system.

Herxheimer Effect.—This was rarely noted in patients treated with triarsen.

Healing of Lesions.—The healing of lesions served, in spite of its comparatively secondary importance from the standpoint of ultimate cure of the disease, as a fair basis of comparison for triarsen with the arsenicals in current use. Table 2 gives a comparison of the healing effect of the new drug with that of arsphenamine, neoarsphenamine, silver arsphenamine and mapharsen as based on the figures given by Cannon, Foerster and their co-workers.

From this tabulation it appears that triarsen stands between neoarsphenamine and arsphenamine in healing efficiency. In comparison with mapharsen, according to the figures given by Foerster and his co-workers and by Kulchar and Barnett, a lesser number of injections and less time to heal primary lesions are required with the new drug, whereas secondary lesions heal in less time but more injections are necessary when mapharsen is used. The small total dosage of mapharsen in grams is in keeping with the small dosage per injection of that drug.

Serologic Effects.—These were in some particulars the most interesting effects from the new drug. Comparatively rapid reversal of a positive Wassermann reaction to negative occurred when it was administered alone and likewise when bismuth was used coincidently. In 78 per cent of 41 patients treated long enough to establish a serologic result, the reaction was reversed after the tenth injection. With triarsen alone reversal to a negative reaction occurred in 41 of 55 patients, and of the 14 in whom the reaction remained positive, 9 received less than 11 injections and the remaining 5 received from 11 to 23 injections.

When a bismuth preparation was given simultaneously with triarsen at weekly intervals there was a slight gain in serologic reversals. In 46 of 71 patients the reaction was reversed to negative, and in 39 of the 46 (84.8 per cent) it was reversed by the tenth injection. Of the 25 in whom the reaction remained positive, 22 received less than 11 injections.

These serologic results compare favorably with the figures reported by the Cooperative Clinical Group, which indicate that continuous treatment with arsphenamine alone reversed the Wassermann reaction of the blood to negative in three months or less in 83.5 per cent of patients while its use with bismuth brought reversal in 30.2 per cent. Our corresponding figures (as nearly comparable as possible) for triarsen are: Administered alone it brought about reversal of serologic reaction in approximately 90 per cent of the patients; with bismuth it caused reversal in approximately 58 per cent in three months or less of continuous treatment (table 3).

Relapse.—Eleven (6.2 per cent) of 177 patients with early syphilis treated with triarsen sustained clinical or serologic relapse. The Cooperative Clinical Group found the total incidence of relapse to be 10.1 per cent. If only the patients treated for six months or longer are considered, the gross incidence of relapse in our cases rises to 8.9 per cent. This compares favorably with the figure (19.7 per cent) given by the Cooperative Clinical Group. Furthermore, the incidence of relapse in patients treated continuously for six months or more with triarsen is 8.5 per cent, as compared with 10 per cent, the figure for those treated intermittently. The latter figure is, however, based on too few observations to be of definite value (2 relapses in 20 treated patients). If our data are further analyzed with regard to the frequency of relapse in

TABLE 3.—*Comparison of Effect of Triarsen with That of Other Antisyphilitic Drugs on the Serologic Reaction of the Blood*

Average Time and Amount of Treatment Required for the Wassermann Reaction to Become Negative in Cases of Primary Syphilis *

Drug	Grams	Injections	Days
Arsphenamine	3.13	7.25	38.2
Neoarsphenamine	5.54	10.10	81.6
Silver arsphenamine	2.17	10.00	59.8
Triarsen	3.46	7.10	55.6
Mapharsen	....	....	43.7

Average Time and Amount of Treatment Required for the Wassermann Reaction to Become Negative in Cases of Secondary Syphilis

Drug	Grams	Injections	Days
Arsphenamine	4.15	10.07	83.4
Neoarsphenamine	7.3	13.80	105.1
Silver arsphenamine	2.51	11.02	112.9
Triarsen	3.92	8.7	88.0
Mapharsen	0.92	?	74.0

* Cannon [13a]; Foerster et al.[14]

patients treated and observed in the early stages of syphilis for any period, it appears that the greatest incidence of relapse occurred in the patients receiving the smaller amounts of the arsenical. Of 74 patients receiving 9 or less injections, 4 had clinical and serologic relapse and 2 had serologic relapse (8.9 per cent). Of 40 patients receiving from 10 to 19 injections, 1 had clinical and serologic relapse and 2 had serologic relapse (7.5 per cent). Of 62 patients receiving 20 or more injections of triarsen, 1 had clinical and serologic and 1 had serologic relapse (3.2 per cent). The Cooperative Clinical Group found the incidence of relapse to be 11.6 per cent, 8.9 per cent and approximately 8.5 per cent, respectively, for the corresponding groups. The results obtained with triarsen are therefore within the limitations of interpretation imposed by smaller numbers as good as, or better than, those given by the Cooperative Clinical Group with reference to relapse and continuous treatment.

The relapses observed in our series consisted of 7 instances of clinical and serologic relapse (2 in 1 patient) and 5 instances of serologic relapse. All the relapses responded to further treatment. We have not encountered any symptomatic neurosyphilis (neurorecurrence) in any of our patients after lapses in treatment.

In attempting to elicit the probable causes of relapse observations were made on the effects of defaulting treatment. One hundred and five patients had absented themselves during their treatment for periods varying from two weeks to two years. Default occurred after from 1 to 29 treatments. If the period of lapse was considerable, the patient was reexamined. Eighty-nine patients (84.8 per cent) showed no apparent effects of these breaks in treatment. Eleven (10.5 per cent) of the defaulters sustained serologic and clinical relapses as stated. Three of the defaulting patients had delayed reversals of the reaction of the blood from positive to negative. In 1 patient the reaction of the blood was reversed from positive to negative during the absence from treatment. One patient was excluded because of lack of data. It is noteworthy that in spite of these lapses no persistent positive reaction was observed.

Effect on the Spinal Fluid.—Of the total of 189 patients, 46 had examinations of the spinal fluid, made as near the sixth month of the duration of the disease as possible. Forty-four of these had absolutely normal fluid; on the 2 abnormal fluids the following observations were made, respectively: In 1 fluid the number of cells was 11, the Kolmer-Wassermann reaction 0122 and the reaction for globulin 1 plus, and the mastic curve was 1111111100. This fluid was examined after the patient had received 24 injections of triarsen and 2 injections of bismuth subsalicylate. In the other fluid the number of cells was 7, the Kolmer-Wassermann reaction 0244, the reaction for globulin 2 plus and the mastic curve 3221100000. This fluid was examined after 6 injections of triarsen and 24 injections of bismarsen had been given. However, after 41 more injections of bismarsen were given the observations on the fluid were as follows: number of cells, 6; Kolmer-Wassermann reaction, 0000; reaction for globulin, 1 plus; mastic curve, 1111100000.

From a summary of this item of the study it appears that of 46 patients whose spinal fluid was examined six months after the beginning of treatment, 10 had had less than 20 injections of triarsen, and only 17 had had treatment equivalent to the category of "much-much" treatment as described by the Cooperative Clinical Group (more than 20 injections of arsenicals and more than 20 injections of heavy metal). In spite of this relatively small amount of treatment, only 4.3 per cent of the patients had abnormal fluid. The figures reported by the Coopera-

tive Clinical Group for control examinations of the spinal fluid in 1,090 patients under observation and treatment of all types of syphilis for two years or more on the basis of the same criteria of abnormal fluid aggregated 33 per cent. Using criteria apparently similar to ours, Gruhzit and his co-workers in 34 fluids examined after 6 courses of treatment with mapharsen and a heavy metal (amount not specified) and a rest period of from two to eight months found 3 abnormal fluids (8.2 per cent). Cannon and Karelitz gave results of 39 examinations of the spinal fluid in observations on 104 patients with early syphilis receiving neoarsphenamine or silver arsphenamine; 7 (18 per cent) had a positive reaction of the fluid and a grade of abnormality much more marked than the pleocytosis and increase in globulin content reported in other cited statistics. The figures given by Zurhelle and Krechel [18] from the clinic in Bonn, Germany, for neoarsphenamine and bismuth subsalicylate give 28 as the percentage of abnormal fluid after 12 injections of each drug, and 7.3 as the percentage after 24 injections of each drug. The latter figure is roughly the equivalent of "much-much" in the categories defined by the Cooperative Clinical Group. It seems then that, again within the limitations of small numbers in the various series cited, triarsen is notably effective, in fact more so than average in controlling asymptomatic neurosyphilis in the early stages of the disease.

Cardiovascular Findings.—Among 26 patients reexamined or seen as late as two and a half years after complete or practically complete treatment, no cardiac or cardiovascular involvement has been noted.

Effect of Triarsen in Pregnancy.—Four previously untreated syphilitic women—3 with early syphilis and 1 with early latent syphilis—were treated with triarsen and bore children who were healthy for at least one year. The mothers received the following treatment, respectively, before delivery: 26 injections of triarsen and 21 injections of bismuth subsalicylate; 11 injections of triarsen and 12 injections of bismuth subsalicylate; 22 injections of triarsen and 6 of bismuth subsalicylate; 20 injections of triarsen and 18 of bismuth subsalicylate. The serologic reaction of the blood in 3 of the patients was positive to some degree at the time of delivery. Two of these patients have again become pregnant. All received additional treatment post partum.

CRITIQUE OF OUR EXPERIENCE WITH TRIARSEN

From our study of triarsen has arisen a clearer conception on our part of what the adequate study of an antisyphilitic drug actually requires

18. Zurhelle, E., and Krechel, J.: Liquorkontrolle maximaler Frühbehandlung mit Vergleichsuntersuchungen bei unbehandelter oder ungenügend behandelter Syphilis: Liquorbeeinflussung durch Malariabehandlung, Dermat. Ztschr. **49**:305-328, 1926.

in the way of material, equipment and facilities for searching inquiry dictated by modern comparative knowledge and practice. The small number of cases on which many of our computations and those of other authors were based clearly indicates that the interpretation of the performance of a drug in early syphilis with respect to relapse and serologic reversal, of the value of a drug under continuous and intermittent technics and of its effects when used alone and in combination with a heavy metal requires either an exceedingly large number of patients or a great deal of time. If the number of patients is very large, the clinical observation inevitably tends toward the hurry-up variety in which the detection of clinical relapse, examination of spinal fluid and follow-up over a long period of time are apt to be sacrificed to the emergency status of having to mill a mob through the machine on each treatment day. It may then properly be asked whether the testing of any drug should be left wholly or chiefly to one clinic, however large. It would be better, we believe, for a group of clinics under central direction or by agreement to farm out portions of the problem for each drug on the basis of the material which each has in greatest abundance—patients with early syphilis for dark field and serologic observation, patients with latent syphilis and persistently positive reaction, patients with congenital syphilis and patients with cardiovascular disease and neurosyphilis. It must be evident that no clinic of average size can undertake the study of two or three drugs simultaneously without publishing sketchy results on one or more of them and that the fiat of a single authority, however weighty, can hardly be accepted as of even preliminary value before observations have been carried out for two or three years.

We feel it particularly important that the testing organization be equipped to make weekly quantitative serologic tests on all patients receiving treatment and that this procedure be not confined to patients receiving the drug tested. We say this notwithstanding the fact that the recent careful work by Moore and his co-workers [19] on comparisons of efficiency of arsenicals in terms of a weekly quantitative serologic test gives the reaction of the blood as such a rather low rating as a guide to ultimate general effectiveness. We were brought sharply to a realization of our need for a weekly test by our inability to make adequate comparisons of triarsen with neoarsphenamine within our own clinical material because we had never as a routine performed serologic tests at each patient's visit during treatment, tests of the blood having been made only on patients receiving the drugs under scrutiny. Thus we have no

19. Moore, J. E.; Hardy, S. M.; Robinson, H. M., and Eagle, H.: The Response of the Quantitatively Titrated Wassermann Test in Early Syphilis to Treatment with Five Different Arsenical Drugs, Am. J. Syph., Gonor. & Ven. Dis. **20**:503-514 (Sept.) 1936.

basis of control within our own clinic and laboratory for the serologic effectiveness of new drugs as compared with the universally used neoarsphenamine. We can compare our results with those obtained in other clinics and on other series of material, but in such comparisons difference in sensitiveness of technic in serologic tests may be so marked as to invalidate the percentage of difference in results. It was found necessary in Martenstein's evaluation of the material studied by the committee of the League of Nations to recognize such a factor of error in comparing the results of treatment reported for Britain and for Denmark, respectively. We are particularly sensitive to the importance of this consideration in evaluating triarsen, because much of its usefulness seems to lie in a specially marked effect on the serologic reaction of the blood. Such an apparent effect may be a pure artefact based on insensitive serologic procedure. While we admittedly lack the absolute control of a universally applied weekly serologic test, we have used all available comparison from other sources in the attempt to see whether the early serologic reversals we observed have real meaning or not.

It is not, therefore, pretended that the study of triarsen here presented is an ideal example of completeness and finality. There are aspects of syphilis it does not touch, and even the examination of effects on the serologic reaction in early syphilis appears in the light of our growing appreciation of test procedure to be incompletely controlled. But it must at least be apparent that the clinical testing of an antisyphilitic drug, especially if it is proposed for general use in treatment of syphilis, or most especially for effective use in early syphilis, demands nowadays facilities and controls seldom applied in work of this sort and not available in much of the material used as evidence by drug-manufacturing houses and clinical authorities at the present time.

SUMMARY

In part I of this study we discussed the outstanding obstacles to adequate clinical testing of drugs to be used in the treatment of syphilis; sales organization influence and competitive tactics; excessive but inescapable costs of research in this field; a disposition to save by inadequate clinical testing and to rush drugs prematurely to the market; noncomparability of toxicity for, and therapeutic efficiency in, animals and man; inadequate contact between clinician (syphilologist) and laboratorian; inevitable slowness and time-consuming nature of research in antisyphilitic drugs; excessively distrustful attitude toward manufacturer on the part of clinical and scientific authority; lack of controlled and defined procedure on clinical as well as laboratory testing; nonrecognition and noncontrol of personal equation elements which are

inevitably operative, and disposition to overexpend so as to cover all variations of syphilis rather than to define or evaluate the field of usefulness of a drug.

In particular, sharp criticism should be directed against the practice of distribution of samples to inexperienced and scattered practitioners, which, while it swells the total number of injections of a drug, provides little in the way of effective and responsible evaluation.

The clinical head of a testing organization is well advised to distrust or to refuse participation in clinical study (*a*) when sales officers' or detail men's influence or hypertrophied sales organization and propaganda are in evidence; (*b*) when direct contact with the head of the manufacturer's scientific organization cannot be had; (*c*) when no adequate information is given as to results of tests on animals; (*d*) when frequent conference, preferably personal, is not possible; (*e*) when the clinical material available is not suitable or is too small or too parceled out among other projects to permit adequate control observations and reports in a reasonable time.

The conditions covering fellowship grants for clinical chemotherapeutic research are enumerated (page 87). These conditions include the following considerations: purpose, amount and duration of the grant, selection of the incumbent, terms governing facilities, reservation of title to facts and interpretations, control of release and publication, rights of the founder, priority in publication and handling of funds through an impersonal agency. All correspondence and communication should be censored by the heads of the manufacturer's research and the participating clinical organizations, respectively. No person, not excepting the research fellow, should be on the staff of both organizations.

The clinical tester of antisyphilitic drugs should on his part accept for test only drugs on which he has the proper material in sufficient quantity; he must have, furthermore, a laboratory equipped for making controlled serologic and dark field examinations, clinical assistants with two or more years' experience, a follow-up mechanism of reasonable effectiveness, a treatment organization maintaining reasonably constant technical performance and reaction incidence and, if possible, a single responsible head for the investigation. Experience with triarsen indicates the need for a routine quantitative serologic test weekly for all patients in the clinic as the proper basis for controlled serologic evaluation.

The clinical evaluation of an antisyphilitic drug should establish (1) the nonexistence of harmful by-effects not identified in tests on animals, (2) the spirillicidal value of the drug in man, no matter what may be the field of treatment for which it is proposed, (3) the incidence of therapeutic shock or Herxheimer effect (4) the rate of healing of

lesions, (5) the symptomatic response of various structures, (6) constitutional effects, (7) the effect on the serologic reaction of the blood, (8) the incidence of clinical and serologic relapse, (9) the reaction and response of the spinal fluid, (10) the evidence of therapeutic paradox, (11) the response and evidence of injury to special organ systems and (12) the value of the drug in cardiovascular syphilis, neurosyphilis, pregnancy and interstitial keratitis.

Additional important considerations include (*a*) strict reduplication of the methods of investigators with the observations of whom comparisons are to be made; (*b*) the handling of patients with infectious syphilis in hospitals until the spirillicidal value of the drug is determined; (*c*) respect for the rights of the patient in not subjecting him to unjustified risk either of reaction or of failure to control his infection; (*d*) a basis of comparison with a standard drug, such as neoarsphenamine, both in the testing clinic and in the literature, by which to judge efficiency from week to week and from month to month as the test proceeds.

The study should provide an answer to the question as to whether the new preparation can be fitted into the now widely publicized schemes of treatment for early syphilis and other aspects of the disease developed from the material of the Cooperative Clinical Group and the League of Nations Health Organization with results as good as those reported for other drugs.

A field of special usefulness may be developed even for a synthetic drug not fitted for use in modern treatment schemes for early stages of syphilis. Conspicuous is the need for (*a*) an especially powerful and rapid spirillicide usable in syphilis resistant to the ordinary arsenicals for sterilizing purposes; (*b*) a drug especially effective in reversing a persistently positive Wassermann reaction; (*c*) a highly effective drug with a wide range of substitution possibilities for other drugs not tolerated by the patient.

A plan for the organization of clinical drug testing on a national scale, with participation of manufacturing, laboratory, academic, clinical syphilologic and governmental control interests and the Council on Pharmacy and Chemistry of the American Medical Association is proposed as a means of reducing the cost and increasing the dependability and disinterestedness of evaluations.

In part II the drug triarsen, an arsphenamine derivative, is considered, both on its merits and as an illustration of the problems discussed in part I. It was investigated by a single observer, on a fellowship grant during four years. Its chemotherapeutic index for animals is 18 as compared with from 6 to 10, the index for effective doses of neoarsphenamine. The drug was given like neoarsphenamine, and 3,009

injections administered to 189 patients, practically all of whom had early syphilis, indicated that it is equal to any of the currently used arsphenamines and to mapharsen as a spirillicide.

The incidence of reactions following the use of triarsen when compared with published figures for arsphenamine, neoarsphenamine and mapharsen indicates that the new drug produces as little reaction of the immediate or mild type as any of these other drugs. Under test conditions it is somewhat more reaction producing than neoarsphenamine administered by the best technic.

There is a possibility that, like sulfarsphenamine, triarsen may produce more dermatitis than neoarsphenamine, but a special circumstance, namely, possible sensitization of patients by preliminary patch tests, in this case requires that judgment be suspended.

Herxheimer effects are rare.

No injuries to special sense organs or to the cardiovascular, hematopoietic or nervous system have been recognized. In 1 patient jaundice developed, the origin of which could not be traced to the drug.

The drug stands second to arsphenamine, is superior to neoarsphenamine and silver arsphenamine and is slightly slower than mapharsen in rate of healing of primary and secondary lesions. While lesions heal in less time when mapharsen is given, more injections are necessary, which makes comparison difficult.

Triarsen has a marked effect on the serologic reaction of the blood in early stages of syphilis. On the basis of a Kolmer complement fixation test and a Kahn and a Kline precipitation test, comparisons with published material indicate that the drug is markedly superior to neoarsphenamine and silver arsphenamine but inferior to arsphenamine in reversing power. The available incomplete data on mapharsen show a slight superiority but do not disclose the comparative number of treatments required. With triarsen 78 per cent of the positive reactions were reversed to negative by the tenth injection. Of 28 patients receiving 20 or more injections of triarsen alone, 3.6 per cent continued to have a positive reaction. Of those receiving 20 or more injections of both the arsenical and a bismuth preparation, 5 per cent continued to have a positive reaction. Part of the apparent superiority may, however, be due to the conservative trend of the tests performed in our laboratory.

The incidence of clinical and serologic relapse in patients treated with triarsen is 6.2 per cent in the aggregate and 8.9 per cent if the observation is continued six months or more. These and the figures for continuous treatment are consistently somewhat better than those given by the Cooperative Clinical Group.

The effect of treatment with triarsen on the spinal fluid in early syphilis, fluid being examined at the sixth month or later, disclosed that

only 4.3 per cent of the patients had abnormal fluid after receiving an amount of treatment aggregating much less than the "much-much" amount described by the Cooperative Clinical Group or the two course treatment with neoarsphenamine and a bismuth preparation described by Zurhelle and Krechel. On the basis of all available comparative figures triarsen is definitely superior to neoarsphenamine, silver arsphenamine and mapharsen in this respect.

The clinical examination of triarsen is incomplete in that its use has thus far been confined practically to early syphilis, and no report is attempted on its use in latent, cardiovascular and congenital syphilis and neurosyphilis.

It may be said in general that triarsen is a new arsphenamine which appears fully equal to the demands of the Cooperative Clinical Group and the international committee (League of Nations) for treatment of early syphilis. Its dermatitis-producing qualities need to be studied and interpreted further, and its apparently striking efficiency with reference to reversal of the serologic reaction of the blood and the prevention of asymptomatic neurosyphilis needs and deserves further investigation.

ULCERATIVE HODGKIN'S DISEASE OF THE SKIN

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The cutaneous manifestations of Hodgkin's disease in general are well known to all dermatologists, as is shown by numerous excellent articles. The ulcerative type of cutaneous lesion seems to have received little attention, however, as only one of a number of standard dermatologic texts consulted mentioned this form. Our interest in the subject was aroused by the following case, which illustrates the difficulty of diagnosis often presented by the ulcerative manifestations of Hodgkin's disease.

REPORT OF A CASE

H. A., aged 23, a cleaner and dyer, was admitted to the Research and Educational Hospital. He stated that he had been in good health until one year before admission, when he noticed that some small "lumps" had developed in the axillae, in the left inguinal region, in the posterior portion of the left auricular region and in the region of the left kidney. The nodules in the axillae and in the retro-auricular region enlarged and in four months reached the size of an orange. His physician gave him some ultraviolet radiation and painted the lesions with tincture of iodine, and the swelling of the retro-auricular glands subsided within a week, while that of the glands in the axillae became greatly reduced. The glands again began to enlarge a few months later and increased in size for the succeeding two months, when an ulcer developed in the right axillary region. This ulcer gradually enlarged, and a biopsy was made three months later. The tissue was taken from the edge of the ulcer, and it was reported that the changes suggested either Hodgkin's disease or sarcoma.

The patient's past and family history revealed nothing of interest, there being no history of tuberculosis or malignant disease. He had been unusually healthy until the onset of the glandular enlargement but had lost 35 pounds (15.9 Kg.) in the seven months preceding entry to the hospital. He also had a productive cough, present only in the morning, and complained of dyspnea on slight exertion. He had suffered progressive weakness until at the time of admission to the hospital he found it difficult to walk.

On physical examination he was found to have a few discrete râles in both lungs. A few discrete slightly enlarged lymph glands were present in the anterior and posterior cervical regions, and the glands in the inguinal regions were moderately enlarged on both sides, being larger on the left than on the right side.

In the right axillary region he presented a well defined deep ulceration of irregular outline with a sharp, somewhat elevated margin. This extended horizontally from the posterior axillary line to the nipple line and vertically from the level of the fourth interspace to the shoulder. The skin was firmly adherent to the underlying tissues. The base was bright red, uneven, friable and covered with a foul-smelling purulent exudate. There was a firm broad zone of induration surrounding the ulcer. The blood count showed 3,440,000 erythrocytes and 20,700 leukocytes; the differential count showed 16 per cent lymphocytes, 6 per cent large mononuclears and transitional forms, 75 per cent polymorphonuclears and 3 per cent eosinophils. The urine was normal; the results of chemical examination of the blood, including determination of the sugar, nonprotein nitrogen and carbon dioxide content, were well within normal limits, and the Kahn reaction was negative.

The patient was difficult to manage, and he left the hospital at the end of a week. While he was hospitalized his temperature varied from 97 to 99.5 F. and showed no special tendency to rise in the afternoon. The pulse rate varied from 80 to 100. He returned eleven days later, having become much weaker at that time. His leukocyte count at the time of the second admission was 34,000, and the differential count showed 21 per cent lymphocytes, 3 per cent mononuclears and transitional forms, 72 per cent polymorphonuclears and 4 per cent eosinophils.

He was given roentgen treatment and then insisted on leaving the hospital, but he was brought back at irregular intervals for further roentgen treatments. Although both the ulcer and the general condition showed improvement in the first two weeks, after that the patient began to decline rapidly. He was unable to retain any food and was so weak that he could not walk without assistance. There was some rigidity of the neck, and the head was held to the right because the induration from the axilla had extended over the chest and up along the right side of the neck. In addition to pain in the ulcer, the patient complained of tenderness on palpation of the infiltrated skin of the neck.

The ulcer now measured only 2¼ by 2½ inches (5.7 to 6.3 cm.), whereas it had measured 4 by 6 inches (10.1 to 15.2 cm.) at the time of the first admission, but the entire right side of the chest showed a boardlike infiltration. In the right supraclavicular space a similar infiltration had developed, the skin overlying it having a mottled red appearance and being painful on palpation. Within two weeks a new small ulcer similar to the large ulcer had developed in the right infraclavicular region.

The patient died three weeks after his last admission. During the last stay in the hospital the same irregular temperature of from 97 to 101 F. was present, and the pulse rate increased from between 82 and 100 to between 100 and 125. At the time he first entered the hospital fluoroscopic and roentgen examination of the lungs showed an average amount of pulmonary markings and no parenchymal infiltrations, while three months later, eighteen days before death, an increase of hilar shadows and linear markings was found, especially on the right side. The report stated that the findings here were consistent with a diagnosis of Hodgkin's disease.

Postmortem Examination.—The body was markedly emaciated. On the right side of the anterior portion of the thoracic wall, extending from the axilla to the fifth intercostal space, was a superficial ulceration which had a ragged margin and a clean granulating base. At the same level below the median third of the clavicle was a grayish-brown fluctuating mass which on section was found to

have a soft yellowish center. Embedded in the subcutaneous fat and muscles were several small grayish pink nodules, apparently lymph glands.

Histologic changes characteristic of Hodgkin's disease were noted in the cutaneous ulcer and in the lymph glands of the anterior portion of the thoracic wall and mediastinum. In the spleen both the pulp and malpighian corpuscles contained numerous swollen reticulum cells which were atypical in form and size and had several nuclei. The other pathologic changes consisted of fibrinous pericarditis with effusion, fibrinous pleuritis, compression atelectasis of the upper lobe of the right lung, cloudy swelling and fatty degeneration of the liver and kidneys, decreased lipoid content and congestion of the adrenal glands and the presence of a small cyst at the tip of the appendix.

The earliest stage of the specific changes could be demonstrated in the lymph glands. In these the normal structure was entirely lost and was replaced by an irregular but generally delicate reticulum. Scattered throughout this were many

Fig. 1.—Ulcerative lesion in the right axillary region of our patient.

swollen endothelial cells which had a small amount of irregularly distributed cytoplasm and a pale vesicular nucleus, the size and shape of which varied in different cells. A few of these cells had several nuclei. There were also many dark-staining small lymphocytes, paler large lymphocytes and a few plasma cells. Everywhere could be seen many newly formed capillaries filled with blood.

Tissue from the surface of the ulcer excised several days before death showed a densely packed infiltration which was composed largely of endothelial cells. These were swollen, showed great variation in size and shape and had a small amount of pale cytoplasm. The nuclei were large, pale and vesicular and showed various shapes, round, oval, club-shaped, elongated and kidney-shaped nuclei being observed. Many of these cells contained large mitotic figures in various stages. There were also many large cells with multilobed nuclei and many multinucleated giant cells of the Reed-Sternberg type. Scattered throughout the infiltrate were many fibroblasts, a few small and large lymphocytes, a few polymorpho-

nuclear leukocytes and few plasma cells; eosinophils could not be demonstrated. Several blood vessels showed a cellular invasion of the wall. A few thickened collagen fibers were present.

The deeper tissue taken from the cutaneous ulcer post mortem showed advanced fibrosis. There were still many circumscribed islands containing a delicate fibrous reticulum. Within these were many elongated fibroblasts with long, dark nuclei and fewer endothelial cells with large, pale, vesicular nuclei. A few lymphocytes

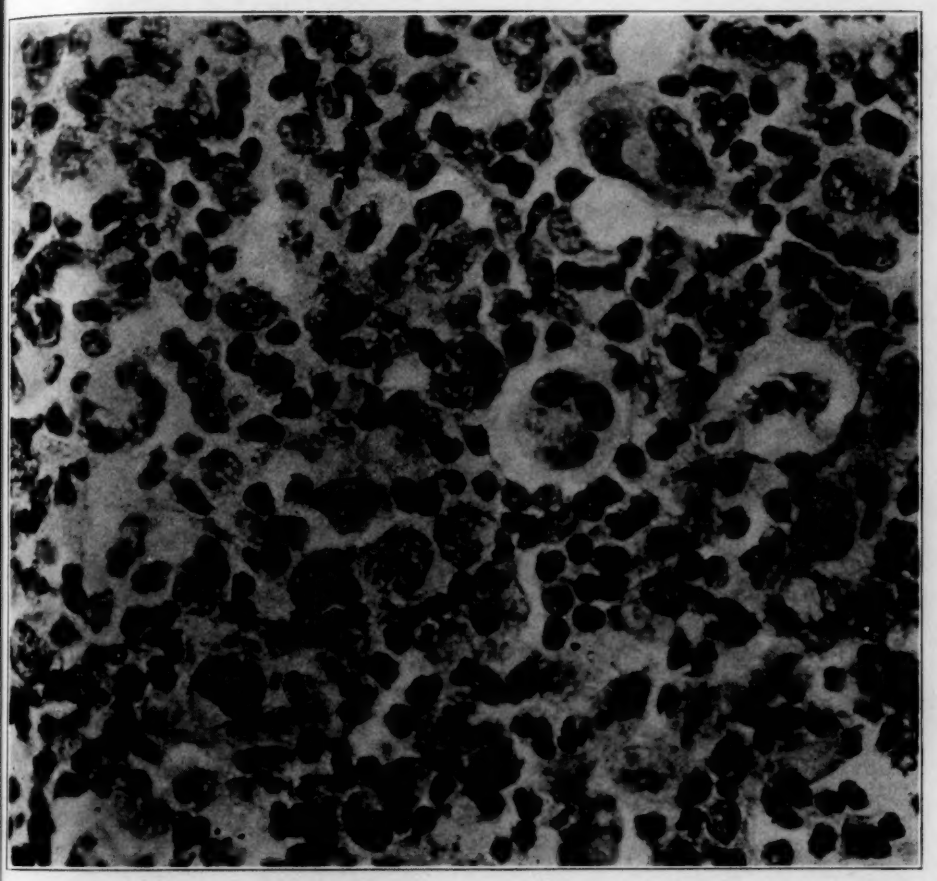

Fig. 2.—Low power magnification of a section taken from the edge of the ulcer.

were still present, but Reed-Sternberg giant cells could no longer be demonstrated. Surrounding these cellular nests lay densely packed strands of relatively acellular and avascular hyalinized connective tissue. Within this fibrous stroma were a few scattered endothelial cells with pale, vesicular nuclei, occasional islands of lymphocytes and several elongated areas of fatty tissue.

The histologic changes present in the various stages of the disease indicated that the condition was an inflammatory process. The replacement of the normal

lymphocytic structures by a granulation tissue composed of proliferating endothelial cells and multinucleated endothelial giant cells and the gradual fibrosis of the granuloma were strong evidence of the presence of some inflammatory agent. The numerous mitotic figures may have signified an active inflammatory rather than a neoplastic proliferation.

In the face of several reports of cases in which a malignant neoplasm occurred in a patient suffering from Hodgkin's disease, one cannot

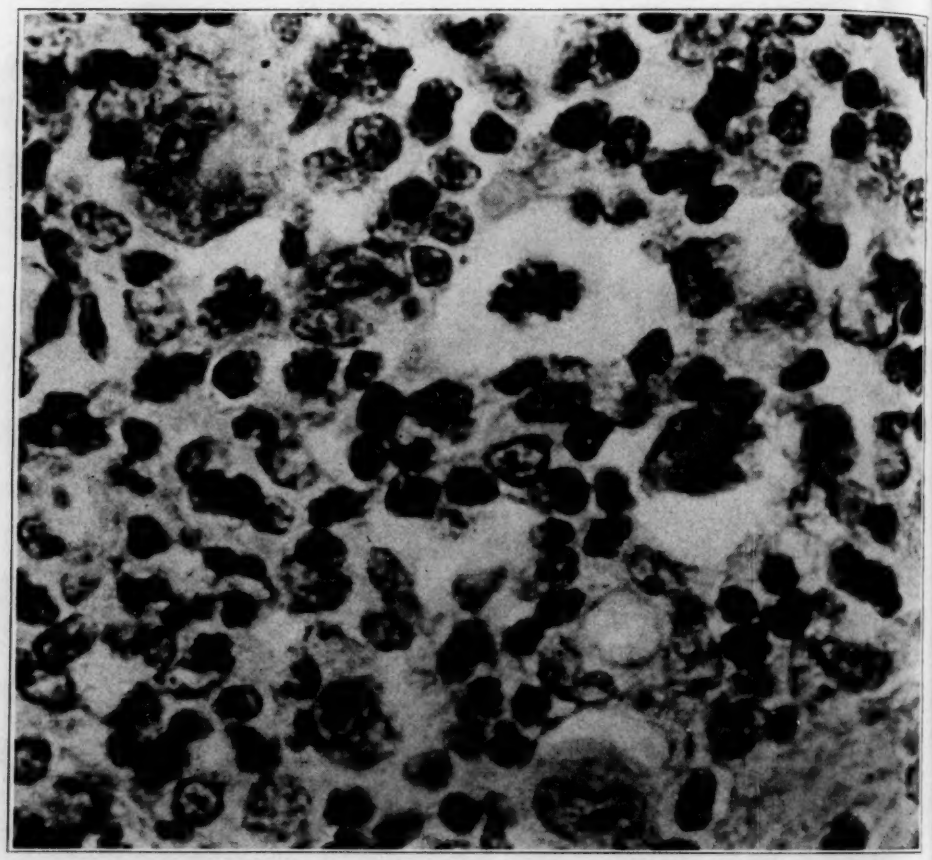

Fig. 3.—High power magnification of a section taken from the edge of the ulcer.

abruptly dismiss the possibility of a sarcomatous supervention in this case. If such a supervention is possible, however, it would be extremely difficult to determine histologically the transitional stage during which the benign proliferation of Hodgkin's granuloma becomes transformed into the malignant proliferation of Hodgkin's sarcoma.

REVIEW OF THE LITERATURE

The first observation of an ulcerative type of lesion in Hodgkin's disease was reported by Grosz [1] in 1906, when he described the first case in which the cutaneous lesions were found to have the specific histologic structure observed in Hodgkin's disease. Since that time about twenty-six cases in which ulcerative lesions were noted have been reported.

In Grosz' case the patient, a man aged 21, presented multiple glandular enlargements, especially in the neck and in the axillae, while the skin of the right side of the face, chest and arm showed a doughy infiltrate. There developed in the skin of the right side of the chest a large number of brownish red tumors from the size of a lentil to that of a walnut, the smaller ones being firm and the larger ones softer. The latter finally broke down at their tips, discharging a bloody serum, and resulted in an ulceration, which finally covered almost the entire surface of some of the lesions, as shown by the illustration accompanying Grosz' article. These cutaneous lesions showed a granulomatous tissue with the presence of Sternberg's cells; the same changes were present in the glands.

Yamasaki [2] described the case of a woman aged 42 who had enlarged glands of the right side of the neck. A huge growth developed there, and similar lesions extended to the right shoulder and axilla and to the left supraclavicular region. An ulceration developed on the right side and extended toward the nape, this lesion resembling an eroding sarcoma.

Cole,[3] in 1917, reported the case of a man aged 37 who had a swelling in the right supraclavicular region which was thought to be an abscess. Later an enlargement of the glands of that region alternately appeared and disappeared, and a diagnosis of Hodgkin's disease was made after one of the glands had been excised. The glands continued to increase in size, and eventually several of them broke down. The skin was then entirely clear except for a large irregularly rhomboid section, 3 by 5 cm., in the right supraclavicular region. This mass showed marked induration and was apparently fused with the glands beneath, while in its center there was ulceration. To the distal side of this area were several lesions the size of a hickory nut, some of which had broken down.

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1. Grosz: Beitr. z. path. Anat. u. z. allg. Path. **39**:405, 1906.

2. Yamasaki, M.: Ztschr. f. Heilk. **25**:269, 1904.

3. Cole, H. N.: The Cutaneous Manifestations of Hodgkin's Disease· Lymphogranulomatosis, J. A. M. A. **69**:341 (Aug. 4) 1917.

In the same year Alderson [4] reported the case of a man aged 28, in whom in 1914 there had developed in the neck and axillae an adenopathy which exhibited a typical microscopic appearance. In June 1916 a painless even oval swelling was noticed along the middle third of the right shin, and a similar hard swelling, apparently connected with the periosteum, appeared in the upper third of the left leg over the tibia. In October 1916 the indurated lesion on the right leg had broken down, forming an ulcer clinically indistinguishable from a gumma. Shortly afterward the lesion on the left leg broke down and formed a similar ulcer. Section of tissue taken from the edge of one of the ulcers showed the condition to be metastatic Hodgkin's disease of the subcutaneous tissue and skin.

Doesseker,[5] in 1919, described the case of a woman aged 54 whose first manifestation was a painless swelling of the scalp, and in whom infiltrations and flat tumors on the forehead near the hair line developed later. There then appeared in various places superficially ulcerating tumors from the size of a walnut to that of a pigeon's egg reminding one of mycosis fungoides. Later the lymph nodes in the occipital region and in the neck became enlarged, and a well defined and deep ulceration developed over the left ear. The author pointed out as unusual features the primary appearance of the tumors, the unusual location, the development of extensive cutaneous changes, the appearance of enlarged glands in the vicinity of the primary outbreak, the absence of typical histologic changes in the skin and the absence of clinically demonstrable glandular enlargements in the beginning of the disease. The diagnosis was made only at postmortem examination.

In the same year Kren [6] recorded the case of a man aged 40 who had a tumor on the right heel. The inguinal glands became enlarged, and the tumor ulcerated and assumed a sarcoma-like appearance. The leg was amputated. Two years later there developed, especially on the extremities, nodes from the size of a hazelnut to that of a walnut, which showed a tendency to ulcerate, and a lesion over the left patella degenerated into a serpiginous ulcer. Again the diagnosis of lymphogranulomatosis was made after autopsy.

Langley's [7] patient was a man aged 24 who had an enlargement of the lymph glands and a large crop of subcutaneous and intracutaneous nodules over the right portion of the thoracic wall, both the gland and the cutaneous nodules showing changes typical of Hodgkin's disease. Within a short time there developed a mass which seemed to arise from

4. Alderson, H. E.: Cutaneous Metastases in Hodgkin's Disease, J. Cutan. Dis. **35**:481, 1917.

5. Doesseker: Arch. f. Dermat. u. Syph. **126**:596, 1919.

6. Kren: Arch. f. Dermat. u. Syph. **125**:561, 1919.

7. Langley, G. J.: Brit. M. J. **1**:667, 1921.

the bone at the second chondrosternal junction on the left side. This grew to half the size of a tangerine, being firmly fixed to both bone and skin. A few weeks later there developed at the back of the neck a mass which seemed to arise from the lower cervical vertebrae, and a nodule the size of a walnut appeared at the right anterior axillary fold. The latter lesion broke down and ulcerated, the ulcer having a crateriform granulating hyperemic surface and a central yellowish slough. The ulcer did not proliferate or fungate, seeming to result more from pressure than from active growth. The diagnosis of Hodgkin's disease was established histologically.

Grossman and Schlemmer [8] reported the case of a man aged 41 in whom after the glands in the clavicular region had become enlarged there developed infiltrated areas on the left arm and knee. These lesions became livid and ulcerated. Later ulcerated lesions developed in the occipital region, on the left side of the neck and on one thigh.

Nanta [9] reported a case in which the localization was unusual, the ulcer appearing at the labial commissure and extending over the cheek.

Saalfeld,[10] in 1924, reported the case of a man aged 52 in whom the glands in the left axilla became enlarged and who later had nodes in the skin of the left side of the chest. The glands in the axilla broke down and suppurated. Eventually the skin of the left portion of the thoracic wall became greatly swollen from the level of the clavicle to that of the nipple, and four coin-sized ulcers developed in the affected part and slowly enlarged. Three of these ulcers reached a considerable size, being irregular in outline and showing slightly elevated margins. Eventually the ulceration exposed the brachial plexus and blood vessels. The diagnosis of lymphogranulomatosis was made on the basis of the biopsy.

Arzt and Randack [11] described three cases in 1925 in which ulceration was a feature. The first patient was a man aged 52 in whom there developed adenopathy in both axillae, followed by cutaneous ulceration with phlegmonous infiltration of the skin of the abdomen and chest. The second patient, a woman, had enlarged glands in the axillae and the submaxillary and supraclavicular regions. The growth in the left axilla became edematous and formed a destructive ulcerating lesion with thickened borders and a base covered with granulation tissue.

In the third patient there developed swelling of the lymph glands in the occipital region with subsequent suppuration. An ulcer formed and gradually increased in extent and depth until finally the entire right side of the scalp and neck was involved, the vessels and bones being

8. Grossman and Schlemmer: Wien. Arch. f. inn. Med. **76**:123, 1922.
9. Nanta: Ann. de dermat. et syph. **3**:519, 1922.
10. Saalfeld: Arch. f. Dermat. u. Syph. **148**:158, 1924.
11. Arzt and Randack: Acta dermat.-venereol. **6**:16, 1925.

exposed. The patient died within a year. Autopsy disclosed lymphogranulomatosis with little involvement of the superficial glands. At the base of the ulcer the occipital bone was nearly destroyed, and the dura was infiltrated by granulation tissue.

In the case of Hirschfeld [12] the picture was similar to that described by Grosz. In the skin of the right clavicular region there developed a group of about twenty brownish red nodules from the size of a pea to that of a walnut. Some of these ulcerated, and as a result of coalescence a saucer-sized ulcer was formed. The nodules showed the pathologic changes typical of Hodgkin's disease.

Linser [13] observed a woman aged 35 who had multiple involvement of the glands associated with the formation of ulcers in the axilla and on the side of the neck and exhibited diffuse ulceration.

Bine [14] recorded a case in which the cutaneous manifestations preceded by many months the other manifestations. In the patient, a woman, there developed nodules in the skin which disappeared spontaneously within a week. Eight months later there developed on the hard palate nodules which broke down and ulcerated, one of them assuming a punched-out character suggestive of a lesion of late syphilis. On the opposite side of the palate was a sloughing lesion which resulted in a perforation, and a slough also appeared in a hemorrhoidal lesion which had existed for a long time. The postmortem diagnosis was Hodgkin's disease of the spleen, liver, kidney, adrenal glands and bone marrow. There were no palpable superficial lymph nodes, but infiltration and necrosis were observed in one lymph gland near the head of the pancreas.

In Sniegowski's [15] case the patient exhibited multiple flat bright red nodes in the skin of the thoracic wall. The center of some of these lesions became necrotic, forming ulcers with an erythematous halo. The ulcers coalesced to involve an area extending from the right axillary to the left mammary line. This was covered in large part by a brownish black crust. The borders were sharp and not undermined.

Mousson's [16] patient was a woman aged 39 who had a generalized eruption resembling mycosis fungoides, followed by the appearance of cervical adenopathy and several large deep ulcers on the left side of the forehead, scalp and shoulder. The ulcers were sharply marginated and

12. Hirschfeld, in Schittenhelm, A.: Enzyklopädie der inneren Medizin. Spezieller Teil. Handbuch der Krankheiten der Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925.

13. Linser: Arch. f. Dermat. u. Syph. **149**:349, 1925.

14. Bine, R.: Am. J. M. Sc. **173**:503, 1927.

15. Sniegowski: Przegl. Dermat. **22**:519, 1927; abstr., Zentralbl. f. Haut.- u. Geschlechtskr. **26**:701, 1928.

16. Mousson: Acta dermat.-venereol. **10**:186, 1929.

deep, presented a dirty base and were surrounded by a flat infiltrated zone. The cutaneous lesions showed the histologic picture of Hodgkin's disease.

Dupont,[17] in 1931, recorded a case of Hodgkin's disease with cutaneous and visceral involvement in which the cutaneous lesions showed histologically the coexistence of typical lymphogranulomatous and tuberculoid lesions. The patient was a man aged 29. He had a group of enlarged glands in the neck, and the left pectoral region was elevated. In the center of this elevation was a palm-sized, irregularly outlined, indefinitely polycyclic plaque made up of nipple-like projections covered by glossy dull red skin. Furrows and depressions, ulcerated here and there, separated the projecting buds.

Gadrat [18] described a case of extensive submaxillary gangrenous ulceration of lymphogranulomatous origin occurring in a man aged 52. In the left submaxillary region there developed a superficial tumor which regressed considerably, but a year later it again began to grow and became more superficial. Ulceration finally took place, being accompanied by discharge of necrotic débris. The ulcer extended rapidly both in extent and depth, forming a large circular lesion, 7 cm. in diameter, with a somewhat elevated border and a base of yellowish necrotic tissue. The appearance was that of a giant rodent ulcer. There was a surrounding zone of infiltration. The histologic picture of the tissue of the ulcer was similar to that in Nanta's case, while the changes in the glands were typical of Hodgkin's disease.

A recent report dealing with the ulcerative type of lesion in Hodgkin's disease is that of Laederich, Mamou and Beauchesne.[19] The patient was a woman who had a fist-sized mass of glands in the right axilla. A year later pea-sized nodes developed deep in the skin of the right scapulothoracic region. In a few weeks these nodules broke down and extended to form two large ulcers, one on the anterior aspect of the right shoulder and one a little below this. These lesions were sharply round, as though the outlines had been traced by a compass. The diameters of the ulcers were 10 cm. and 4.5 cm., respectively. The borders were elevated, showing a padlike margin, and the bases were soft, uneven and covered with a greenish fetid pus.

In addition to these cases there should be cited an unpublished case mentioned by Chevalier and Bernard [20] in which the ulcer was in the perineal region and one of Milian's [21] in which in a patient with a

17. Dupont: Ann. d'anat. path. **8**:929, 1931.

18. Gadrat: Ann. de dermat. et syph. **3**:917, 1932.

19. Laederich, Mamou and Beauchesne: Presse méd. **41**:277, 1933; Bull. Soc. franç. de dermat. et syph. **39**:1363, 1932.

20. Chevalier and Bernard: Maladie de Hodgkin, Paris, Masson & Cie, 1932.

21. Milian: Bull. Soc. franç. de dermat. et syph. **39**:241, 1932.

cutaneous disorder suggesting early mycosis fungoides there developed extensive cervical and subclavicular tumors, many of which ulcerated. The borders of these ulcers showed the presence of innumerable cells of the Sternberg type. In addition Milian [22] referred to another case, that of a woman in whom after the opening of tuberculous glands at the base of the neck there developed an excavating ulcer the size of a small hand; biopsy of material from the border disclosed a granuloma with typical Sternberg cells.

Etienne, Drouet, Florentin and Louyot,[23] in 1933, described the case of a woman aged 35 in whom two large ulcers appeared in each cervical region after the development of a fistula resulting from breaking down of underlying glands due to Hodgkin's disease. The ulcers had rather sharp violaceous contours, and the margins were everted on the healthy skin surrounding them.

Fanielle and Neujean,[24] in 1934, described the case of a man aged 32 who had had a painful swelling over the sternum two and one-half months earlier. This swelling increased in size and then broke down to form an ulcer the size of a 2 franc piece, which apparently resulted from the coalescence of two smaller ulcers. The base of the lesion was irregular, bled easily and was painful to the touch. The underlying bone was eroded. Biopsy of material from one of the enlarged glands and from the margin of the ulcer showed a typical picture of Hodgkin's disease.

The cases in the literature have been thus abstracted in order to emphasize the wide variety of clinical pictures which may be produced by ulcerative lesions in Hodgkin's disease and to bring out their importance in differential diagnosis.

Chevalier and Bernard [20] pointed out that cutaneous tumors are not seen frequently in Hodgkin's disease and that while they may at times appear at the beginning of the disorder, they more often complicate the typical course of the disease. They further stated that the distribution of these tumors is irregular and that they are never generalized, predominating in the region of the breasts, on the back and near the attachments of the extremities. They are sometimes isolated, sometimes grouped and rarely confluent. The neighboring tissue may be normal or diffusely infiltrated. Chevalier and Bernard stated that unlike the nodules in leukaemia cutis, the tumors in Hodgkin's disease have a tendency to ulcerate. Gadrat pointed out that observations of extensive ulceration in lymphogranulomatosis are rare. Louste and Levy-

22. Milian: Bull. Soc. franç. de dermat. et syph. **39**:1362, 1932.

23. Etienne, Drouet, Florentin and Louyot: Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1144, 1933.

24. Fanielle and Neujean: Liége méd. **27**:889, 1934.

Frankel [25] spoke of ulceration as being exceptional in tumors of this disorder, while Laederich and his co-workers found that the ulcerative form was considered exceptional by French dermatologists, although there have been rather numerous references to it in publications in the literature of other countries.

COMMENT

Ulceration may be said to occur in Hodgkin's disease in three different ways. The first is the type in which there are a number of cutaneous or subcutaneous nodules showing the typical histopathologic structure, in some of which ulceration develops (case of Grosz and case of Hirschfeld). In this type the necrosis usually begins on the top of one of the nodules and gradually extends to cover the surface of the nodule more or less completely. These lesions may remain discrete or may coalesce to form larger ulcers, as in the case of Hirschfeld.

In the second type the skin is affected as a result of involvement secondary to lymphogranulomatous changes in underlying structures, as in the case of Cole, in which the cutaneous infiltrate was apparently fused to a mass of enlarged glands beneath, in the case of Alderson, in which the gumma-like lesions were connected with the underlying periosteum, and in the case of Dupont, in which the thoracic ulcer was directly connected with the enlarged glands in the mediastinum. Gadrat expressed the belief that in cases of this type the massive destruction of tissue is of glandular origin, the glands having literally poured out their lymphogranulomatous infiltrate into the deep layers of the skin, the tissues being eventually destroyed by necrosis. The skin is thus undermined and destroyed just as are bones and muscles in Hodgkin's disease.

In the third form there develops in the skin, either as the primary manifestation of the disease, or subsequent to, but not as a direct extension of glandular involvement, large infiltrates or tumors rather than the small nodules which characterize the first variety. The case of Doesseker, that of Kren and that of Saalfeld are examples of this type. In both the second and the third type the ulcers are as a rule extensive.

It is particularly with these larger ulcerations that we are concerned, because it is when they are present that the greatest confusion in differential diagnosis is likely to arise. This is particularly true in cases in which the infiltration and subsequent ulceration develop before an enlargement of the palpable lymph node areas is apparent.

The ulcers usually develop and extend rapidly up to a certain point; then extension ceases or is slow.

The ulceration may present a variety of forms. The fully developed lesions vary in size from that of coins to that of the one exhibited by

25. Louste and Levy-Frankel: J. méd. franç. **17**:19, 1928.

Arzt's patient, which covered most of the right parietal and occipital regions of the scalp and extended on to the neck. The borders are as a rule sharply defined but may vary in outline from the geometrically round ulcers in the case of Laederich and his co-workers to an irregular outline, as in Saalfeld's case; they may even be mangled in appearance as in Arzt's case, or serpiginous, as in the case of Kren and in that of Nanta. In Cole's case the ulcer took a linear form. As a rule the margins are elevated; often they show a somewhat padlike elevation, as in Gadrat's case.

The margins may be undermined and flabby or sharply punched out to resemble a gumma, as in the cases of Bine, of Alderson and of Kren. Usually the ulcers are deep and have an uneven floor covered with abundant purulent or necrotic material or granulation tissue. The base, as a rule, is soft. In most cases there is a fetid odor.

In some cases the ulcers develop in a large plaque of infiltration, as in the case of Cole and in that of Dupont, while in others they develop from the breaking down of underlying glands, after which an extensive infiltration of the tissues surrounding the ulcer may take place (as in Gadrat's case, in the case of Arzt and in our case). In our case this secondary infiltrate covered almost the entire right side of the chest.

As a rule the ulcers bleed freely when touched. Pain of variable degree, at times severe, is usually present.

A review of the cases reported from the standpoint of the areas affected by ulcerative lesions shows the incidence of involvement to be as follows: neck, six cases; thorax, four cases; axillary region, four cases; clavicular region, three cases; chest and neck, three cases; neck, knee and arm, one case; scalp, one case; forehead and scalp, one case; buccal mucosa, one case; labial commissure and cheek, one case; lower extremities, two cases; perineal region, one case. Scattered lesions were present in two cases. The figures show that in cases in which the ulceration occurs as a single lesion or as multiple lesions in a restricted area the submaxillary, clavicular, axillary and thoracic regions are most frequently affected, these regions being involved in twenty-one of the twenty-seven cases.

From a review of the cases in which the age of the patient was given it was found that the youngest patient was 23 and the oldest 52 and that the average age was 36. The span of life from the first signs of the disease to death varied from a few months to four and one-half years, the average span being about two years. The incidence according to sex was about 2.3 male to 1 female, which is exactly in keeping with the ratio for Hodgkin's disease in general as stated by Wallhauser.[26]

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26. Wallhauser, A.: Hodgkin's Disease, Arch. Path. **16**:522 (Oct.); 672 (Nov.) 1933.

DIFFERENTIAL DIAGNOSIS

The difficulty of diagnosing the ulcerative form of Hodgkin's disease is emphasized by a perusal of the various case reports, for in many instances diagnosis was made only after biopsy or postmortem examination. Among early suggested diagnoses of the ulcerative lesions were syphilis, sarcoma, mycosis fungoides, epithelioma and tuberculosis. Laederich and his co-workers have recently discussed the differential diagnosis; they pointed out that in syphilis the base of the ulcer is not as a rule purulent, there is no tendency to hemorrhage and the neighboring glands are not enlarged. The serologic reactions and the therapeutic test are also of value. In tuberculous ulcers the thin violaceous and undermined margins and the irregular outlines present an appearance differing from that of the ulcers in lymphogranulomatosis. The type of large tuberculous ulcer of the skin described by Darier [27] and more recently by Pautrier [28] may, however, present a close resemblance to a lesion of lymphogranulomatosis.

The resemblance to epithelioma may be great in some lesions, and biopsy may be necessary to establish a differentiation, although the exceptional involvement of the face by lymphogranulomatous ulcers and the frequency of basal cell cancer in that location are significant. Leukemic lesions of the skin ulcerate rarely, but when they do the concomitant signs of leukemia and the blood picture usually serve to differentiate them from lymphogranulomatosis.

Laederich and his co-workers emphasized the difficulty of distinguishing between the ulcers of Hodgkin's disease and those of mycosis fungoides and pointed out that the clinical resemblance is so great that it brings up again the question as to whether Hodgkin's disease and mycosis fungoides are not identical. They joined Ziegler, Milian and many others in supporting this idea. Mycosis fungoides was considered as a probable clinical diagnosis in at least four of the cases reviewed here.

The occurrence of these ulcers has also been of importance in the discussion as to whether or not sarcoma may be engrafted on the inflammatory tissue of Hodgkin's disease or whether the inflammatory proliferation may take on malignant characteristics. In some of the earlier cases reviewed the ulcers were regarded as sarcomatous, but in the later cases they have generally been held to be purely lymphogranulomatous. Gadrat found that in the cases in which ulceration was present the alterations of inflammatory and of neoplastic type constituted a singular complex which made it easy to understand how in a large number of cases lesions of Hodgkin's disease have been interpreted as neoplasms.

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27. Darier, cited by Pautrier.[28]
28. Pautrier: Ann. de dermat. et syph. **3**:785, 1932.

Nanta and Chatellier,[29] who expressed the belief that there is often an inoculation lesion in Hodgkin's disease, supported this theory by citing cases in which an ulcerative lesion was seen as the first manifestation of the disorder; they used Kren's case, in which the first lesion was an ulcer on the heel, as an example of this theory.

CONCLUSIONS

1. The ulcerative type of Hodgkin's disease of the skin is relatively uncommon, about twenty-seven cases, which are briefly reviewed here, having been reported.

2. The ulceration may occur in three different ways, the processes being as follows: (*a*) ulceration of limited extent developing in a number of small nodules in the skin; (*b*) extensive ulceration developing in the skin by extension from underlying involvement of lymph glands, bones and other tissues; (*c*) extensive ulceration developing in large infiltrations appearing in the skin without involvement of the underlying structures.

3. Ulcers may be single or multiple and may vary greatly in size and shape. They usually bleed freely when touched and as a rule are painful.

4. The submaxillary, clavicular, axillary and thoracic regions are most commonly affected, although no part of the body is exempt.

5. These ulcers are of great importance from the standpoint of differential diagnosis, as they may simulate closely the lesions of syphilis, sarcoma, mycosis fungoides, epithelioma and tuberculosis.

6. The ulcerative lesions usually develop after the glandular involvement has become apparent, but in some cases they have furnished the primary evidence of the disease.

7. The histopathologic picture in tissues removed from the ulcerative lesions is usually characteristic of Hodgkin's disease, the number of Reed-Sternberg cells varying greatly in different cases. In some instances no typical changes are apparent, and the picture may be strongly suggestive of sarcoma.

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29. Nanta and Chatellier: Ann. de dermat. et syph. **6**:682, 1925.

EXTERNAL CAUSES OF DERMATITIS

A LIST OF IRRITANTS

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In 1930 I published in the ARCHIVES a list of cutaneous irritants.[1] This article is an outgrowth of that report. It undertakes to cover all substances which have been reported to cause cutaneous irritation, and the record is brought up to Aug. 1, 1936. The arrangement of the irritants has been changed from that of the first article, in which they were grouped under various classes. Experience seems to show that it is better and more convenient to give an alphabetical list of all irritants. I have given the name of each irritant approximately the way it was designated by the author cited. There are therefore some repetitions and inconsistencies. The U.S.P. term or the term used by the American Medical Association Press has been inserted in parentheses after the original designation whenever possible. I have also given a list of irritants according to occupations in which such irritants are encountered, so that the physician can easily locate the irritants to which a certain patient may be exposed. These two lists, I believe, will greatly simplify the search for irritants causing dermatoses.

The main purpose of the lists is to enable one to locate the irritant in specific cases, and no extensive attention has been paid to symptomatology or other features. But under "comment" are given salient characteristics of the irritants or of the reactions. After one has made a diagnosis, one can get full information from standard textbooks on cutaneous diseases. These lists are given specifically for the purpose of diagnosis. The number with each item designates a reference to the literature on the subject. Much of the information has been obtained from the work of R. Prosser White [2] and from that of James C. White [3]

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1. Weber, Leonard F.: A List of Cutaneous Irritants, Arch. Dermat. & Syph. **21**:761 (May) 1930.

2. White, R. Prosser: The Dermatoses or Occupational Affections of the Skin, ed. 4, London, H. K. Lewis & Co., 1934.

3. White, James C.: Dermatitis Venenata: An Account of the Action of External Irritants upon the Skin, Boston, Cupples & Hurd, 1887.

It should be pointed out that the fact that a substance is occasionally irritating is not sufficient to bring a general indictment against that substance. Many substances which occasionally produce irritation in a sensitized person do it so seldom that this disadvantage is justly disregarded in the face of great advantage which the substance may have for its purposes. For example, there is hardly any perfume that does not produce dermatitis, but it does not do so frequently enough to justify the banishment of all perfume.

I Sources of Cutaneous Irritation

Cutaneous Irritants	Comment
Abiurana [4]	
Acetate of iron (iron acetate U. S. P.)	
Acetic acid (White, R. P.,[2] p. 128)	Burns Used by hat makers, bottle cleaners and bronze cleaners Wood turpentine contains 4% acetic acid
Acetic acid vapors [5]	Employed in trades using lacquers, varnishes, cements, colors and india rubber containing acetone
Aceto—arsenite of copper, emerald green, meadow green, English green, patent green, parrot green, Schweinfurt, or Kaiser green	Used in the manufacture of aceto-arsenite
Acetone (White, R. P.,[2] p. 128)	Used in lacquers, varnishes, cement and india rubber solution
Acetylene gas	Dermatitis in persons employed in the manufacture of it
Acid bichromate	
Acid calcium phosphate ($CaHPO_4$)	A flour improver; cakes and confectionery are made with a mixture containing acid calcium phosphate Acid calcium phosphate irritates during hot weather
Acid chrome	
Aconitum napellus (monk's-hood) (White, J. C.,[3] p. 117)	Redness and vesicles Working the plant for aconitia often produces severe dermatitis
Acridine	The principal basic constituent of crude anthracene A strong cutaneous irritant either in liquid or in solid form
Acronycta xylinoides (White, J. C.,[3] p. 199)	Irritating action caused by the pricks of the spines
Actinic rays	From sun, electric arc and other sources of rays; ultraviolet rays from quartz lamps
Adoneta spinuloides (White, J. C.,[3] p. 199)	Irritating action caused by the prick of the spines
Adhesive plaster [6]	Causes two types of reaction, one purely chemical and due to the maceration and mechanical trauma resulting from the application and the removal of the plaster and the other due to hypersensitivity to one or more of the ingredients of plaster The chief irritants are the resins, beeswax, olibanum, hydrous wool fat, orris and gutta siac
African ebony [4]	Used in turnery and inlaying
African mahogany [4]	Used in cabinet work, furniture and interior trimming
African padouk [4]	Used in furniture and decorative panels
Allanthus glandulosa (tree of heaven) (White, J. C.,[3] p. 125)	Disagreeable odor during flowering season
Air, compressed	Mechanical abrasion
Alisma plantago (water-plantain) (White, J. C.,[3] p. 31)	Leaves contain an acrid principle that irritates

4. Senear, F. E.: Dermatitis Due to Woods, J. A. M. A. **101**:1527 (Nov. 11) 1933.

5. Carozzi, L.: Acetic Acid, in Occupation and Health, Geneva, International Labour Office, 1919, no. 33.

6. Schwartz, L., and Peck, S. M.: Irritants in Adhesive Plaster, Pub. Health Rep. **50**:811 (June 14) 1935.

Cutaneous Irritants	Comment
Alcohol (wood)[7]	Reaction on hands
	Printers clean plates with alcohol; wood alcohol used in making "collodion and acetate of cellulose" silk; according to the duco method of painting the metal surface is first rubbed or cleaned with alcohol and phosphoric acid; in a walking-stick factory methyl alcohol is a source of irritation
	Pure alcohol does little damage to the skin
Alder wood	
Alizarin	Used in synthetic dyestuff factories
Alkalis	Alkalis are a frequent cause of dermatitis and cause reddish pigmentation of the skin and hair; with slight friction they remove the corneous layer; they penetrate deeply and destroy extensively
	Weak acetic acid should be applied to a wound from strong alkali
	Solid caustic soda (sodium hydroxide) and solutions of caustic soda of moderate strength if hot destroy clothing, skin and mucous membranes; solid caustic soda and solutions of caustic soda are used for general detergent purposes and largely in chemical, soap and grease, textile and washing industries; alkalis form the basis of many patent cleaners. Coopers use alkalis in barrel washing; alkalis are used in wool manufacture; the wool washers are exposed to the caustic and irritating action of alkaline solutions; in enamel works alkaline mixtures are required as scourers; woods used in architectural joining are soaked in caustic potash (potassium hydroxide) solution; in furniture and lavatory covers factories use caustics and alkalis; cleansing material often causes itch due to alkali; in the nickel-plating trade "alkali itch" is common
	Powdered soap used by grinders, weighers and packers causes irritation from caustic soda
	Water glass (sodium silicate) used in soap making, paper sizing and manufacture of washing compounds, as preservative for eggs, in carboard factories, in concentrated solution for making immovable bandages and cases used by surgeons; box works use sticker with silicate
	Potassium cyanide used in cleaning silver and gold and in removing silver nitrate stains from cloth
	Potassium cyanide used by engravers, watch makers, silver polishers, men working in brass foundries and foundry and bronze and copper workers
Allium sativum (garlic) (White, J. C.,[3] p. 102)	
Allspice (White, J. C.,[3] p. 111)	Redness
Almond oil[8]	Used in soaps
Aluminum salts and dusts[9]	Irritation of the skin and mucous membranes is produced through mechanical action
	Materials used in grinding, buffing and polishing aluminum ware, "soda ash" caustics, benzine, stearic acid, turpentine, tripoli, nitric acid, sulfuric acid, silica carbide, aluminum oxide, metallic aluminum dust, emery and pumice stone
Amber (bakelite)	
Amber liquid (stryacifiua)	
Amidophenyl mercaptan vapors	
Ammonia aqua (aqua ammonia U. S. P.) (White, J. C.,[3] p. 156)	Applied lightly to the skin it dissolves the epithelial layer, but if allowed to remain long in contact it produces an erythematous or vesicular inflammation
Ammonia (diaper)[10]	Reaction in the gluteal region
Ammonium bichromate[11]	Ulceration

7. Turner, J. A.: Acute Dermatitis Among Painters Employed in an Industrial Plant, J. Indust. Hyg. **7**:293, 1925.

8. Coca, Arthur F.; Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C. Thomas, Publisher, 1931.

9. Possible Trade Dermatitis, Queries and Minor Notes, J. A. M. A. **94**:2085 (June 28) 1930.

10. Cooke, J. V.: Etiology and Treatment of Ammonia Dermatitis of Gluteal Region of Infants, Am. J. Dis. Child. **22**:481 (Nov.) 1921.

11. Smith, A. R.: Chrome Poisoning with Manifestations of Sensitization, J. A. M. A. **97**:95 (July 11) 1931.

Cutaneous Irritants	Comment
Ammonium carbonate (concentrated) (White, J. C.,[3] p. 157)	Mild dermatitis
Ammonium chloride	
Ammonium nitrate (White, R. P.,[2] p. 267)	Powder causes mild dermatitis
Amyl acetate	
Amyl acetone	
Amyris wood [4]	Source of West Indian sandalwood oil
Anacyclus pyrethrum [12]	Used in the manufacture of insect powder Gardener carrying the plant had dermatitis
Andaman padouk [4]	Used in interiors of pullman cars, decorative panels and pianos
Andira araroba (goa powder) (White, J. C.,[3] p. 106)	The dust is irritating Goa powder used in medicine
Andiroba [4]	Used in furniture, house construction and ship building
Angelica tree (White, J. C.,[3] p. 174)	The green bark is irritating to the hands of collectors
Aniline dyes [13]	Used in face powder and rouge
Aniline oil [14]	Pustular lesions on the scrotum and various parts of the body Reported as irritating in the rubber industry; Prosser White did not think it irritating
Anthracene	
Anthralin (dihydroxyanthranol)	
Antilles satinwood [4]	Used in cabinet work and decorative work
Antimony	Papules and pustules on the hands Affects workers at the melting-pots used for type; occupational dermatitis from antimony is rare; antimony as a mordant in the dye of a fur has caused a dermatitis when fur was worn
Apothesine [15]	Cutaneous reactions to apothesine and quinine in susceptible persons
Arbor vitae (White, J. C.,[3] p. 90)	The fresh leaves irritate
Aristol (thymol iodide U. S. P.)	
Arnica (tincture of)	Redness, papules and vesicles, usually confined to the area to which the drug is applied but sometimes extending Arnica plant contains formic and angelic acids and a volatile oil
Aroeira [4]	Used in construction
Arsenic	Erythema, papules, vesicles, pustules and ulcers, localized or generalized Arsenic is excreted particularly by the sweat glands, causing follicular changes The urine should be examined for arsenic Arsenic is used in paper, fancy and surface colored, sheets, covering of carboard boxes, labels of all kinds, advertising cards, wrappers and cases of sweetmeats, ornamentation of children's toys, covering of children's and other books and for lamp shades Arsenic is used in combination with aniline and other dyes in the preparation of wall and other colored papers, in printed and dyed clothes, in artificial flowers, as a preservative of sizings and pastes and for curing hides and bird skins
Arsenic trioxide [16]	
Artichokes	
Artificial silk	
Asparagus [17]	Edematous patches covered with papules and vesicles on the hands and arms Asparagus juice is the irritant; workers in an asparagus-canning factory had dermatitis; sugar is also a factor
Asphalt	
Atlas satinwood [4]	Used in cabinet work
Atropine	

12. McCord, C. P.; Kilker, C. H., and Minster, D. K.: Pyrethrum Dermatitis, J. A. M. A. **77**:448 (Aug. 6) 1921.

13. Miller, H. E., and Taussig, L. R.: Cosmetics, J. A. M. A. **84**:1999 (June 27) 1925.

14. Quinby, R. S.: Health Hazards in the Rubber Industry, J. Indust. Hyg. **8**:103 (March) 1926.

15. Mook, W. H.: Skin Reactions to Apothesin and Quinin in Susceptible Persons, Arch. Dermat. & Syph. **1**:651 (June) 1920.

16. Irvine, H. G., and Turnacliff, D. D.: Study of Group of Handlers of Arsenic Tri-Oxide, Arch. Dermat. & Syph. **33**:306 (Feb.) 1936.

17. Halberg, V.: Five Cases of Asparagus Dermatitis, Hospitalstid. **75**:1235 (Oct. 20) 1932.

Cutaneous Irritants	Comment
Atropine [18]	Reaction in workers in the production of apo-atropine
Aurantia (cheap shoe dye)	
Australian blackwood [4]	Used in cabinet work, joinery and motor car bodies
Australian silky oak [14]	Used in furniture and parquet flooring
Automobile wheel (varnish)	Reaction on the hands
Avertin fluid [19] (tribromethanol in amylene hydrate)	Erythematous reaction on the fingers and palms Used as a general anesthetic Dermatitis occurred in an anesthetist
Bakelite (amber) [20]	Contains phenol-formaldehyde condensation resins From 6 to 10% methendiamine may be added Bakelite irritates more often in summer, when perspiration is profuse Vapors arising during baking can be irritating
Baking [21]	Baker's dermatitis reaction on exposed parts The active irritant is the low grade mechanical injury from dough followed by mycotic infection; sources of irritation are: flour, potassium persulfate (flour improver), calcium sulfate in confectioners' flour, cream of tartar (potassium bicarbonate), salt, sugar, bran, acarids, wetness, wheat protein (sensitization to), yeasts and fungi; ammonium persulfate is mentioned as an injurious agent
Balm of Gilead (White, J. C.,[3] p. 130)	Erythema, edema and bullae Present in liniments applied to the skin after cuts and bruises
Balsam of peru (peruvian balsam U. S. P.)[22]	Brilliantines are perfumed with synthetic perfumes or peruvian balsam
Baneberry	Vesicles The plant is common in the northern states
Barley [23]	Barley itch Caused by parasitic acurus Occurs in handlers of barley, especially in dock workers
Barley pollen [24]	Erythematous vesicular reaction The pollen is probably the active irritant
Bassia wood [4]	Used in ship building, construction and manufacture of agricultural implements
Bastard lignum vitae [4]	Used in bearings or brushing blocks, pulley sheaves, bowling balls and backs of brushes
Bath salts	
Bayberry (White, J. C.,[3] p. 111)	A fragrant oil used in bay rum
Bay rum (White, J. C.,[3] p. 113)	A popular wash for the scalp and face
Beef fat [25]	Reaction on the hands
Beeswax [26]	
Beet sugar	
Beggar ticks (White, J. C.,[3] p. 87)	
Benetol	
Benzine [27]	Vesicles on the hands and arms and interdigital clefts of the second, third and fourth fingers are characteristic of the reaction to benzine in the rubber industry Painters use benzine for removing paint from the arms and hands

18. Herxheimer, K.: Ueber die gewerblichen Erkrankungen der Haut, Deutsche med. Wchnschr. **38**:1822, 1912.

19. Kulchar, G. V.: Contact Dermatitis in an Anesthetist, Due to "Avertin" (Tribrom-Ethanol), J. A. M. A. **99**:560 (Aug. 13) 1932.

20. Sachs, O.: Dermatitis Among Workers in Phenol Resins, Wien. klin. Wchnschr. **34**:356 (July 21) 1921.

21. Zitzke, E.: Allergic Nature of Baker's Eczema, Dermat. Wchnschr. **95**: 1009, 1932; abstr., J. A. M. A. **99**:1210 (Oct. 1) 1932.

22. Cummer, C. L.: Dermatitis Produced by Balsam of Peru, Arch. Dermat. & Syph. **16**:44 (July) 1927.

23. Pascal: Brit. J. Dermat. **13**:37, 1901.

24. Hodara, M.; Behdjet, H., and Sureya: Dermat. Wchnschr. **76**:209, 1923.

25. Frank, Louis J.: Contact Dermatitis Due to Beef Fat, Arch. Dermat. & Syph. **32**:629 (Oct.) 1935.

26. Umansky: Dermatitis in Beekeeper Caused by Sensitivity to Beeswax, Dermat. Wchnschr. **98**:177 (Feb. 10) 1934.

27. Dermatitis from Benzine, Queries and Minor Notes, J. A. M. A. **84**:1377 (May 2) 1925.

Cutaneous Irritants	Comment
Betanaphthol	Peeling of the skin Often used in ointments for cosmetic purposes to produce peeling of the skin
Betel nut [28]	Reaction on the lips Siamese women chew betel nut
Bichromate and solutions	Erythematous papular reaction on the hands, arms, face and neck Used in printing and mordanting of wools In any room in which a bichromate is employed, vessels containing a solution of sodium bisulfate should be at hand for cleansing the hands, as this reduces the bichromate to harmless compounds; the hands should be rinsed thoroughly with water
Bichromate of potassium, potassium bichromate (White, R. P.,[2] p. 326; Parkhurst [29])	Superficial ulceration of the fingers of blue-print dippers in the blue-print industry
Biniodide of mercury (sodium iodide and ammoniated mercury)	
Bismarck brown	A shoe dye ingredient
Bitter orange [30]	Erythema, vesicles and pustules on the face and left hand of workmen engaged in peeling oranges
Black alder [4]	Used in drain pipes, ply, veneer, card and cigaret cases
Black bean [4]	Used in furniture, interior work and carving
Black cotton shirts	
Black hellebore (White, J. C.,[3] p. 120)	Vesicles
Bleeding heart [31]	
Bloodroot (White, J. C.,[3] p. 115)	The root is sharply irritating
Blue-print (potassium bichromate)	
Bookbinding	Glue and formalin (solution of formaldehyde U. S. P.) are the irritants
Borage (White, J. C.,[3] p. 78)	Reaction on the hands Cultivated in gardens; used in salads
Borax (sodium borate U. S. P.) [32]	Chronic dermatitis Irritant to gatherers and users
Boric acid [33]	Prolonged use of boric acid has repeatedly led to dermatitis
Borneo cedar [4]	Used in furniture, paneling and construction
Borneo rosewood [4]	Used in ornamental work and fine furniture
Boxwood (White, J. C.,[3] p. 93)	Used in ox yokes, house construction, boat building and piles
Bracelet made of ebony [34]	Reaction on the wrist
Brauna [4]	Used in heavy construction, vehicles and floorings
Brazil or red satinwood [4]	Used in furniture and cabinet work
Brazil wood,[4] dye wood	
Brazilian rosewood [4]	Used in furniture, cabinet work, billiard tables and phonograph cabinets
Brazilian walnut wood	Redness of exposed parts
Brickyards (White, R. P.,[2] p. 201)	Pustular lesions on the inner surfaces of the hands, arms, thighs and legs if the oil soaks into the clothing Oil is the irritant
Brigalow spearwood [4]	Used in turnery, fancy ware and cabinet making
Brine baths	Papular reaction occurring at health resorts
Briquet making	
Bromine trifluoride	
Bronze	
Brown-tail moth (Euproctis chrysorrhoea) (White, R. P.,[2] p. 411)	Mild or severe, limited or extensive reaction In May and June this insect is found in all parts of Europe except in the extreme north

28. Mendelson, R. W.: Tinea Labialis, J. Trop. Med. **27**:284 (Nov. 1) 1924.

29. Parkhurst, H. J.: Dermatosis Industrialis in a "Blue Print" Worker Due to Chromium Compounds, Arch. Dermat. & Syph. **12**:253 (Aug.) 1925.

30. Murray, F. A.: Dermatitis Caused by Bitter Orange, Brit. M. J. **1**:739 (May 21) 1921.

31. Harville, C. H.: Contact Dermatitis Due to a Common Plant, J. Allergy **4**:527 (Sept.) 1933.

32. Hazen, H. H.: Industrial Skin Diseases, J. Cutan. Dis. **32**:487, 1914.

33. Cushny, Arthur R.: A Textbook of Pharmacology and Therapeutics, or the Action of Drugs in Health and Disease, ed. 5, Philadelphia, Lea & Febiger, 1910, pp. 585-586.

34. Nicolas, J., and Pétouraud, C.: Dermite eczématiforme du bras à la suite du port d'un bracelet d'ébène, Bull. Soc. franç. de dermat. et syph. **42**:27 (Jan.) 1935.

Cutaneous Irritants	Comment
Brucella [35]	Follicular involvement of the forearms and hands of veterinary surgeons
Bunion protector (rubber) [36]	Reactions on parts to which the protector is applied
Burdock (White, J. C.,[3] p. 87)	A weed common in most parts of the United States
Burma lacquer [4]	
Burma padouk [4]	Used in planks, beams and decorative work
Burwood marsh elder [37]	
Butchering [38]	Butchers' dermatitis; erythematous vesicles on hands, starting on the webs of the fingers and spreading to the sides and backs of the fingers and to the backs of the hands as far as the wrists, occurring in butchers and inspectors who handle carcasses of freshly killed animals
Butesin picrate [39]	
Buttercups (White, J. C.,[3] p. 120)	Redness
Butyn [40]	
Calcium chloride [41]	Reaction on exposed parts and where clothing is soaked Used in spraying coal to keep down the dust Impurities in the calcium chloride are the likely irritants
Calcium hydrate	
Calcium hypochlorite	
California cedar [4]	All types of hardwood
Camel hair [42]	
Camomile (wild) [43]	Reaction on the hands and feet of laborers in flax fields Camomile is mixed with flax plants
Camphor [44]	
Canada pitch (White, J. C.,[3] p. 89)	Redness, papules and pustules Applied to the skin in the form of a plaster
Canadian spruce [4]	Used in paper manufacture, construction, crates and boxes
Candy	The chief irritant is sugar; essential oils, used as flavoring agents, occasionally cause dermatitis; chocolate containing a potassium salt may be irritating
Canoe birch [4]	Used in turnery
Cantharides, plaster and tincture [45]	Men suffer reaction in the making of cantharides plasters
Cantharides, powder (White, J. C.,[3] p. 197)	When applied to the skin the powder produces a violent dermatitis
Carasco (Puerto Rico)	A source of dye
Carbide	
Carbolic acid (phenol U. S. P.) (White, J. C.,[3] p. 148)	Erythematous papular reaction over wide areas Diluted phenol as generally used in dermatologic therapy is capable of producing irritation
Carbon disulfide	

35. Weber, Leonard F.: Brucella Dermatitis, Arch. Dermat. & Syph. **26**:422 (Sept.) 1932.

36. Niles, Henry D.: Dermatitis Due to Rubber Bunion Protector, J. A. M. A. **97**:778 (Sept. 12) 1931.

37. Huber, H. L., and Harsh, G. F.: Summer Dermatitis Caused by a Common Weed, J. Allergy **3**:578 (Sept.) 1932.

38. Schwartz, B.: Butchers' Dermatitis, J. Indust. Hyg. **13**:233 (Sept.) 1931.

39. Pusey, W. A., and Rattner, H.: Dermatitis from Butesin Picrate, Arch. Dermat. & Syph. **19**:917 (June) 1929.

40. Greenwood, Arthur M.: Butyn Dermatitis, J. A. M. A. **83**:1077 (Oct. 4) 1924.

41. Calcium Chloride and Dermatitis, Queries and Minor Notes, J. A. M. A. **95**:1198 (Oct. 18) 1930.

42. Ramirez, M. A., and Eller, J. J.: "Patch" Test in "Contact Dermatitis" (Dermatitis Venenata), J. Allergy **1**:489 (Sept.) 1930.

43. D'Agostino, M.: Flax Dermatitis, Semana méd. **34**:642 (Sept. 8) 1927; abstr., J. Indust. Hyg. **10**:71 (March) 1928.

44. Sutton, I. C.: Acute Dermatitis from the Wearing of "Horn-Rim" Spectacles, J. A. M. A. **89**:1059 (Sept. 24) 1927.

45. Oppenheim, M.: Gewerbliche Hautkrankheiten, Wien. klin. Wchnschr. **27**: 63, 1914.

Cutaneous Irritants	Comment
Carbon paper (hectograph) [46]; some types of ink; indelible pencil leads	Aniline dyes are the active irritants
Carbonate of ammonia (ammonium carbonate U. S. P.) (concentrated solutions) (White, J. C.,[3] p. 157)	Mild dermatitis
Carbonate of potassa (potassium carbonate) (White, J. C.,[3] p. 157)	Redness and papules
Card table cover [47]	
Carpoglyphus passularum [48]	Figs covered with it are irritating
Cashew nut (White, J. C.,[3] p. 71; Neubauer [49])	Irritation caused by cardol, a redish, oily liquid of neutral reaction and slight aromatic color used for coloring, or preserving vanilla pods and for marking clothing in laundries
Castor oil (Coca;[3] Karobow [50])	It is possible that dermatitis can result from contact The duration of the dermatitis is always short
Catalpa (White, J. C.,[3] p. 77)	Redness Flowers are irritants
Caustic calcium hydrate (White, R. P.,[2] p. 165)	Dermatitis first; then necrosis Wet hands or skin liberate it from carbide
Caustic potash (potassium hydroxide U. S. P.)	
Caustic soda (sodium hydroxide U. S. P.)	
Cedar wood [8]	A wood extractive which may cause contact dermatitis
Celandine (White, J. C.,[3] p. 115)	Redness and vesicles The fresh juice is irritating
Celery juice [51]	Reaction on the hands and forearms of a celery picker
Celluloid substitutes that were polished (White, R. P.,[2] p. 250)	"Artificial amber" and horn are made of this nature Polish consisted of 0.15% solution of formaldehyde with acetic acid, ammonia, "soda" and sodium sulfite
Cement	
Cercazia elvae [52]	
Chalk (colored) [53]	Reaction on the face and ears Dust caused the dermatitis
Chamomile (camomile)	Reaction on the hands and feet A weed causing dermatitis in flax gatherers
Chestnut	Thickening of the skin of the hands Used in construction
Chinese primrose	Used for decorative purposes
Chloral hydrate [54]	Erythematous papular reaction One drachm (3.69 Gm.) of chloral hydrate to a pint (473 cc.) of alcohol is capable of producing irritation when "sopped" on the skin two or three times a day
Chlorate of potassium (potassium chlorate U. S. P.) (White, R. P.,[2] p. 133)	Used by munition workers in the making of electrolytically produced potassium chlorate Electrolyte must be warm and alkaline
Chloride of platinum (platinum chloride (White, J. C.,[3] p. 175)	Papules
Chloride of sodium (hot solution)	Reaction on the palmar surface of the left thumb and index finger and on the flexor aspect of the left forearm in flax spinners and soakers
Chloride of zinc (zinc chloride U. S. P.) (White, J. C.,[3] p. 172)	

46. Dermatitis from Carbon Paper, Queries and Minor Notes, J. A. M. A. **101**:1903 (Dec. 9) 1933.

47. Niles, H. D.: Case Report: Dermatitis Due to Card Table Cover, New York State J. Med. **36**:113 (Jan. 15) 1936.

48. O'Donovan, W. J.: Dermatitis Due to Carpoglyphus Passularum, Brit. J. Dermat. **32**:297 (Oct.) 1920.

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54. Cited by White,[3] p. 154.

Cutaneous Irritants	Comment
Chlorinated lime, solutions of..... (White, J. C.,[3] p. 162)	Redness and papules affecting workmen employed in bleacheries and paper mills
Chlorinating plant ..... (White, R. P.,[2] p. 227)	The active irritants are ethylene and tetrachlorethane
Chlorine ..... (White, R. P.,[2] p. 162)	Redness, papules and vesicles
Chocolate[55]	Affects chocolate dippers, roasters and candy makers who handle chocolate
Christmas rose ..... (White, J. C.,[3] p. 120)	Vesicles
Chrome ..... (White, R. P.,[2] p. 149)	Affects those who come in contact with the hot solutions; dermatitis occurs among workers stirring the fluid in the keeves and workers in the crystal house
Chromic acid ..... (White, J. C.,[3] p. 172)	Ulceration of the hands and arms In the manufacturing process and use chromic acid is irritating
Chromium (potassium bichromate, ammonium bichromate, chromic acid)	Used in chromium plating, in stainless lithography and photolithography and in tanning
Chromium compounds ..... (White, R. P.,[2] p. 150)	Used in photographic and lithographic processes and in the manufacture of the bichromates
Chromium-plated articles[56]	Parts in contact affected Reaction caused by wearing of wrist watches, metal bracelets, garter and shoe buckles, necklaces and spectacle frames
Chromyl chloride vapor ..... (White, R. P.,[2] p. 151)	Reaction on the hands Used for electric deposition of chrome to make metals rustless
Chrysanthemum leaves[57]	Erythematous reaction, generalized and more severe on the exposed parts, in a greenhouse employee
Chrysarobin	From the wood of a Brazilian tree, Andira araroba
Cinchona bark	
Cinnamon powder[58]	Vesicles on the mucous membranes Seldom irritates the skin
Citrine ointment (ointment of mercuric nitrate U. S. P.) (White, J. C.,[3] p. 170)	Redness, papules and vesicles Used in the treatment of inflammatory and noninflammatory conditions of the skin
Citrus wood[4]	Used in hubs and felloes of cart wheels
Clematis.....	Redness and vesicles The juice of the plant is irritating
Cloth handling ..... (White, R. P.,[2] p. 321)	Dermatitis due to imperfect washing out, neutralizing or cleaning of the various materials in the dyed fabric Reaction occurs in persons who handle cloth such as tailors, shirt makers, cloth clerks, cloth makers and cloth pressors
Clothing[59]	Reaction on the hands and arms due to colored articles of clothing next to the skin; irritation from the presence of zinc chloride in the clothing
Coal tar lubricating oil ..... (White, R. P.,[2] p. 221)	Reaction on the hands, forearms, neck, face, abdomen and thighs from screw nuts dipped into the oil
Cocklebur (clotbur) ..... (White, J. C.,[3] p. 89)	Irritation from the dust with which the bur is covered
Coco-bolo[4]	Used in handles of knives and tools, backs of brushes, inlay, and bowling balls
Cocoa butter (theobroma oil U. S. P.) (White, R. P.,[2] p. 273)	Irritation in persons working in cocoa butter factories Used in pomades, salves, cold creams, vanishing creams and fine soaps, as base of ointments and as base for suppositories
Coconut oil[8]	Used in the manufacture of soap
Cocus wood[60]	Persons working with the wood are affected Flutes are made from this wood
Coleus plant	Reaction on exposed parts A patient of mine had dermatitis from the plant

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Cutaneous Irritants	Comment
Collier work [61]	Reaction in external auditory canal due to irritation from particles of stone and coal; colliers work in a reclining position
Colored paper [62]	Reaction in a school girl
Colza oil	Used for polishing gold chains
Common parsnip [63]	
Composing (printing) (White, R. P.,[2] p. 282)	Compositors clean type with gasoline or benzine and trichlorethylene
Copper (dermatitis) [64]	Irritation from dust containing copper
Copper [65]	Copper itch
Copra dust	Irritation from dust containing copper
Coral sumac or mountain machineel (Rhus metopium)	Reaction on the arms The fresh juice is irritating The tree grows in tropical America
Corn or maize oil [8]	Dermatitis results only from external contact with the flour
Cornet (silver plated)[66]	The lips become dry and fissured Reaction caused by long and repeated pressure on the players' lips
Corrosive sublimate (mercury bichloride U. S. P.)	
Cosmetics (Cole;[67] Goodman [68])	
Bleaches	
Freckle bleach	
Harriet Hubbard Ayers bleach	
Lemon cream bleach	
Face bleach	
Creams	
Freckle cream	
Stillman's freckle cream	
Harriet Hubbard Ayers freckle cream	
Pompeian night cream	
Lemon and glycerin cream	
Lemon cream	
Harriet Hubbard Ayres cold cream	
Powder	
Face powder	
Talcum powder	
Armon's powder	
Hudnut's liquid violet talcum	
Aeolian rouge face powder	
Rouge	
Rouge	
Lipstick	
Lipstick (Armon's)	
Miscellaneous	
Black and white ointment	
Mercolized wax	
"Marcirillo"	
Slendaform flesh reducer	
Grease paint	
Elmo	

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68. Goodman, Herman: Skin Reactions to Combinations of Two Toilet Articles Neither of Which Alone Caused Irritation, Arch. Dermat. & Syph. **32**:632 (Oct.) 1935.

Cutaneous Irritants	Comment
Cotton seed [69]	Used as an upholstering material Contains potassium bichromate
Cotton velvet	Redness and papules on the forearms
Courbaril [4]	Used in carpentry and general construction
Cowhage (Mecuna pruriens), a climbing tropical plant [70]	The dry commercial product is irritating Used as a vermifuge
Cow parsley (angelica) when cut green (White, R. P.,[2] p. 364)	Vesicles Used for candying a sweetmeat
Cow parsnip (White, J. C.,[3] p. 136)	Vesicles The leaves are irritating
Cow parsnip [71]	The irritant is acrid sap contained in the outer root and rind The plant grows extensively in southern Europe
Creosote (White, J. C.,[3] p. 148)	Redness
Croton oil (White, J. C.,[3] p. 94)	Redness and papules
Cyanide [72]	Potassium cyanide used for case hardening and tempering metals may be treated with cyanide baths; cyanide used in mill plants where cyanide process of gold extraction is done Irritation may be from strong caustics rather than from cyanide; lime is the exciting agent
Daffodil stock [73]	Reaction on the hands of pickers and packers of flowers
Daisies (King Edward daisies, ox-eyed daisies)	Reaction on the left elbow and wrists after picking peas The plants occur in meadows
Daphne Mezerun (White, J. C.,[3] p. 132)	Redness All parts of the plant produce irritation
Deerskin gloves [74]	Erythema of the hands and wrists due to wearing of gloves
Dental amalgam [75]	
Deodo and odorono [76]	Irritation from aluminum salts
Depilatories	Barium and calcium sulfide are irritants
Dermax (turkey red oil)	
Dichloramine-T	
Dictamnus fraxinella [77]	Irritation from exposure to the stalks, leaves or flower
Dinitrochlorbenzene [78]	Used in the manufacture of dyestuffs
Dionin (ethylmorphine hydrochloride U. S. P.) [79]	Reaction on lids
Dragon-root (White, J. C.,[3] p. 73)	Redness and vesicles caused by the fresh leaves and roots

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74. Parkhurst, Howard J.: Dermatitis Venenata Due to Deerskin Gloves, J. A. M. A. **19**:301 (July 23) 1932.

75. Blumenthal, Franz, and Jaffe, K.: Amalgamplomben als Ursache von Quecksilberdermatitis, Deutsche med. Wchnschr. **55**:1720 (Oct. 11) 1929.

76. Dermatitis from Deodorants, Queries and Minor Notes, J. A. M. A. **104**: 674 (Feb. 3) 1935.

77. Baronovysky: Russk. vestnik dermat., January 1929, p. 58.

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79. Cummer, C. L.: Dermatitis of the Eyelids Caused by Dionin, Arch. Dermat. & Syph. **23**:68 (Jan.) 1931.

Cutaneous Irritants	Comment
Dry cleaning [80]	Reaction varies with the length of time the dress that has been cleaned is worn; when a short-sleeved dress is worn the reaction occurs in the axillary folds, sternum and neckline; when a long-sleeved dress is worn the antecubital fossae are also affected The active irritants are carbon tetrachloride and trichlorethylene
Duco [81]	
Dust in the broom-making industry [82]	Dermatitis from the mechanical irritation of the dust
Dwarf juniper [4]	Used in turnery
Dyanshine (a shoe dye and polish) [83]	Reaction on the feet and legs The active irritant is bismarck brown
Dye manufacture	The following chemicals are known irritants: acids, sulfonic anthraquinone, chlorinated anthracene (silver salt), alphanaphthylomic acid amino-azobenzene, benzidine, benzanthrone, betamethylamino-anthraquinone, bismarck brown, beta oxynaphthoic acid, benzoylpara-aminophenol, betahydroxynaphthoic acid aniline, benzoylbenzylic acid, brombenzanthrone, betanaphthol, cresol, chlorbenzene, chloraniline (para and ortho), dinitrobenzene, dinitrophenol, dinitro-anisol, d'hydrothiometaxylidine, dichloraniline, dinitrotoluene, dinitrochlorbenzene, formic acid, guanidine, indophenol, isorosinduline, Mischler's hydrol, metatoluenediamine, methylanthraquinone (chlor and beta), nitraniline (para and meta), napthylamine (alpha and beta), nitrobenzene, nitrodimethylaniline, naphthalene nitrobenzanthrone, nitrosodiethylaniline, nitrobetamethylanthraquinone, orange R, thiazole, orthonitrotoluene, orthonitrochlorbenzene, ortho-aminophenol, phenylhydrazine, phenylhydrazineparasulfonic acid, phtholic anhydride, phenylamino-acetic acid, paratotylnitrile, paranitrisophenyl, paranitro-ortho-aminophenol, paranitrochlorbenzene, paranitrotoluene, polysulfide, para-aminophenol, resorcinol sodamind, toluene and toluidine
Dyestuff, synthetic	Active irritants are alizarin aniline acid
Earphones of wireless sets [84]	Reaction on the ears of persons wearing receiver Irritation from the rubber or the varnish
East Indian satinwood [4]	Used in furniture, backs of brushes, panels and veneer
Egg white (shampoo) [42]	
Electroplating work [85]	Finishers suffer from lime
Electrotyping	Reaction due to lye used to wash the graphite and dust
Elm [4]	
Embuia [4]	Used in furniture, cabinet work, interior trim and construction
Emerald green	
Emeraude perfume [86]	Erythematous reaction caused by perfume sprayed on a dress
Emetine solution [87]	Redness, papules, vesicles, pustules and urticaria on the forearms and hands of pharmacists
Enamel works (White, R. P.,[2] p. 131; Dolgow [88])	Erythema to ulcerations on the hands and forearms and changes in the nails Irritants: enamel and its filtrate, and solution of nickel sulfate and cobalt Used in porcelain and pottery factories

80. Hollander, Lester: The Hazards of Dry Cleaning, J. A. M. A. **102**: 66 (Jan. 6) 1934.

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82. Piccini, P.: Lavoro **12**:136 and 166, 1920.

83. Possibility of Bismarck Brown as Cause of Dermatitis from Dyanshine, Queries and Minor Notes, J. A. M. A. **96**:212 (Jan. 17) 1931.

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88. Dolgow, A.: Sovet. vestnik dermat. **9**:114 (Feb.) 1931; abstr., Arch. Dermat. & Syph. **24**:1089 (Dec.) 1931.

Cutaneous Irritants	Comment
Engineering works (White, R. P.,[2] p. 217)	Irritants: cooling and lubricating mixtures containing turpentine and alkaline emulsions of mineral oil; shale oil is the injurious compound
English mass (White, J. C.,[3] p. 90)	Reaction on the hands of gardeners The plant is used as an edging for beds in flower gardens
Engraving material (White, R. P.,[2] p. 293)	The irritant is potassium cyanide used on silver and gold
Ephedrine [89]	Reaction on the nose and face from ephedrine contained in nasal sprays
Ethyl acetate	A patient of mine had dermatitis from ethyl acetate
Ethylene chloride	
Eucalyptus hemiphoia (Australian gum tree) [90]	Irritation by contact, and in some instances even by proximity
Euphorbia corollata (snake milk) (White, J. C.,[3] p. 96)	Redness and vesicles
Euphorbia ipecacuanha (White, J. C.,[3] p. 96)	The plants are irritating to those who collect and handle them
Euphorbia lathyris (White, J. C.,[3] p. 96)	
European oak [4]	General use
Eyelash curler [91]	Erythema, papules and vesicles on the upper and lower eyelids Rubber on the curler is the irritant
Face lotions [92]	Eyelids
Facial cream [93]	The ingredient causing dermatitis was methylheptine carbonate; it is used commercially for producing artificial violet and jasmine odors in facial cream
Feathers [8]	
Felt hat	
Fertilizers	
Ferula galbaniflua (White, J. C.,[3] p. 186)	
Fig [4]	
Flaxseed (hair tonic) [42]	Linseed oil is made from flaxseed; the oil is employed in the manufacture of soft soap
Fleabane (White, J. C.,[3] p. 87)	Common weed found in all parts of North America The fresh plant is irritating
Flit (insecticide) [94]	
Flour mills [95]	No cases of dermatitis in flour mills
Flutes' beaks made of coco-bolo wood and grenadilla [96]	Reactions on the faces of flute players
Flute playing (White, R. P.,[2] p. 304)	Irritation of the mouth from the resinous contents of the mouth-piece, which is made from grenadilla wood
Flytox [97]	
Formaldehyde	
Formalin (solution of formaldehyde U. S. P.)	Reaction on the hands and forearms; often an excess in soap will start a dermatitis on the hands and feet The preparation is handled by pharmacists and pathologists
Formic acid (White, J. C.,[3] p. 153)	Violent dermatitis due to concentrated formic acid
Formosa (lacquer tree) [4]	
Friction tape [98]	

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92. Rattner, H.: Dermatitis of the Eyelids, J. A. M. A. **103**:180 (July 21) 1934.

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95. De Jong, Oscar: Etiology of Dermatitis in Bakers, Lancet **1**:894 (May 5) 1923.

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97. Osborne, E. D., and Putnam, E. D.: J. A. M. A. **99**:972 (Sept. 17) 1932.

98. Schwartz, L., and Albaugh, R. P.: Dermatitis in Nut and Bolt Plant Due to Use of Friction Tape, Pub. Health Rep. **49**:1051 (Sept. 7) 1934.

Cutaneous Irritants	Comment
Fuchsin	Reaction due to fuchsin used in dyeing of stockings and marine blue gloves
(White, R. P.,[2] p. 143)	
Fur	The irritant is usually paraphenyldiamine A list of the chief dyes used is as follows Light brown—pyrogallol Medium brown—metatoluene diamine base Dark brown—metaphenylene diamine base Red brown—para-amidophenolchlorhydrate Deep black—paraphenylene diamine Blue black—aniline black and aniline black with paraphenylene diamine In the preparation of the furs the hair is first cleansed of grease by means of soda, soap, lye mixed with ammonia or milk of lime. To increase the affinity of the hair, it may be soaked in bleaching powder and hydrochloric acid. For dyeing, one of the amines commercially known as "ursol," "furol," "fantol," etc., is used. When darker shades are required, the skins are first mordanted with potassium bichromate or with the sulfates of iron and copper. The mordants are not neutralized in the cheap furs, and therefore it is suspected that the strong chemicals used as well as the dyes themselves may produce dermatitis
Furfurol[99]	Used in cleaning cellulose paint from metal surfaces
Furniture polish	Reaction in the forks of the fingers and on the knuckles
(White, R. P.,[2] p. 285)	Pyridine and methyl alcohol are the active irritants
Fustic[4]	Used in wheels, carpentry and fence posts and as fuel
Gaillardia	Exposed parts are affected The specific irritant is an oil The flower is found in the United States from March to late fall; florists and housewives handle it
Garden nasturtium	
(White, J. C.,[3] p. 133)	
Garden rue	Redness and vesicles
(White, J. C,[3] p. 127)	The leaves irritate; handlers have trouble with the green plant
Garget	The green plant and the root are irritating
(White, J. C.,[3] p. 116)	
Garlic	Redness and vesicles
(White, J. C.,[3] p. 102)	Garlic bulbs are applied as a counter irritant to the chest in pulmonary diseases
Gasoline, ethyl[100]	
Geranium[101]	
Glass wool[102]	
Gloves (black)[103]	
Glue	Glue is used on old book covers and in making furniture Cabinet makers and violin makers may be affected
Godfrey's dye[92]	Reaction on the eyebrows and eyelashes
Golden rod	Reaction on hands
(White, J. C.,[3] p. 89)	A volatile oil is the irritant
Gold melting	The active irritant is heat arising from melting precious metals in crucibles
Goncalo alves[4]	Used in furniture and parquet flooring
Goose feathers[104]	
Granadilla	Used in musical instruments, such as flutes and clarinets, and in parquetry inlay, backs of brushes and handles of knives
Grapes[105]	In order to produce a reaction it is necessary to eat grapes as well as to get the grape substance on the skin

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100. Johnson, David W.: Dermatitis Caused by Ethyl Gasoline, Arch. Dermat. & Syph. **28**:174 (Aug.) 1933.

101. Anderson, James W.: Geranium Dermatitis, Arch. Dermat. & Syph. **7**: 510 (April) 1923.

102. von Szentkirályi, S.: Dermatitis Due to Glass Wool, Dermat. Wchnschr. **93**:1302 (Aug. 15) 1931.

103. Simon, C.: Dermatitis Due to Black Gloves, Bull. méd., Paris **47**:168 (March 11) 1933.

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105. Anderson, J. Mercer: Dermatitis from Grapes, Arch. Dermat. & Syph. **31**:658 (May) 1935.

Cutaneous Irritants	Comment
Gray gum box [4]	Used in railroad sleepers, posts, pilings, mauls and handles
Green dragon (White, J. C.,[3] p. 74)	
Greenheart [4]	Used in general construction and ship building
Guao [4]	Obtained from Cuba
Guinea-pig hair [106]	A source of dye
Gypsum and plaster wall board [107]	Folliculit...
Hairdressing materials [108]	Erythema and scaliness of the interdigital webs Preparations for setting hair contain the following ingredients: tragacanth, linseed gum, quince seed gum, karaya gum, boric acid, sodium, potassium and ammonium carbonates, alcoholic keratin, coloe, petrolatum, cera-flux, glyco wax A, paraflux
Hair dyes [67]	
Barbo comp	
Black dye	
Brownatone	
Depotts	
Eau sublime	
False hair dye	
Golden Glint	
Henna	
Inecto	
Inecto rapid no tox	
Kolor-Bak	
Lux (imported)	
Perfecto	
Rapidol	
Wyeth's sage and sulphur	
Youth-o-lede	
Hair tonic (wildroot) [109]	Redness and swelling of the eyelids The patient's husband used the hair tonic; it was transferred through the medium of a bolster The preparation contains arsenic, phenolic body, probably resorcinol and alkaloid material and alcohol
Hair tonics [110]	The hands of barbers may be affected
Hair tonic [67]	
Auxiliator (Westphal's)	
Danderine	
Farr's "hair vim"	
Hair restorer	
Henna (shampoo)	
Herpicide	
K. D. X.	
Liquid arvon	
Lucky tiger	
Mahdeen	
Mascara	
Quinine	
Quinine resorcinol	
Wildroot	
Hair oil (White, R. P.,[2] p. 273)	
Hat bands (artificial leather) [111]	
Hay and straw	
Heat [112]	Hyperpigmentation in a man exposed to the heat of the rolling mills of an iron works Dermatitis can follow hypersensitivity to heat

106. Markley: Anaphylactoid Dermatitis Due to Direct Contact with Animal Epidermal Structures, Arch. Dermat. & Syph. **2**:722 (Dec.) 1920.

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109. Hollander, Lester: Dermatitis of the Upper Eyelids Due to the Use of a "Hair Tonic," J. A. M. A. **97**:1384 (Nov. 7) 1931.

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Cutaneous Irritants	Comment
Hedge mustard	Redness and papules
(White, J. C.,[3] p. 91)	
Helenium microcephalum [113]	The irritating substance is oleoresin
Hemlock spruce	Resin from it is called Canada pitch
(White, J. C.,[3] p. 89)	If applied to the skin in the form of a plaster it is irritating
Hemp	
Henna [114]	
Hexanitrodiphenylamine [115]	An explosive material
Hexylresorcinol [116]	An antiseptic used in tooth paste and as a household remedy
Hop [111]	Hop pickers have trouble during September
Hop hornbeam (a plant) [117]	
Horn-rimmed spectacles [44]	
Horseradish	
(White, J. C.,[3] p. 91)	
Horseweed	The fresh plant is irritating
(White, J. C.,[3] p. 87)	
Human hair (transformation)	The dye is irritating
Humea elegans	A gardener brought Humea elegans to Chicago in 1930
Hyacinth bulbs [118]	Reaction on the distal ends of the fingers of a clerk in a bulb and seed store
Hydrocyanic acid	
Hydrofluoric acid	
Hydroquinone (quinol)	Reaction on the fingers
(White, R. P.,[2] p. 294; Northcote [119])	Used for developing
Hymolal salts [120]	Reaction on the hands
(a soap-like material composed of sulfonated alcohols of high molecular weight)	The preparation is a soaplike material composed of sulphonated alcohols of high molecular weight combined with an alkali to form the neutral salt
	Hymolal salts is used as a shampoo
Hypochlorites	
Ichthyol (sulfonated bitumen) [42]	Reaction caused by shaving cream containing ichthyol
Icy water	Affects fish salters, who stand in icy water several hours a day
Indian bean	Redness
(White, J. C.,[3] p. 77)	
Indian jungle wood [4]	Used in furniture, house building and turnery
Indian rosewood [4]	Used in pianofortes and furniture
Indian tobacco	
(White, J. C.,[3] p. 110)	
Indian turnip	Redness and vesicles
(White, J. C.,[3] p. 73)	The leaves and roots are irritating
Indo-Chinese lacquer [4]	
Inecto hair dye	
Ink poisoning [121]	Printers with dry skin suffer from reaction; those with oily skins are immune
Insect powder [122]	Irritant if it contains Anacyclus pyrethrum
	Certain chrysanthemums are used in insecticides
	A gardener carrying Anacyclus pyrethrum had dermatitis on the arms

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116. Cummer, Clyde L.: Dermatitis from Use of Hexylresorcinol Solution S. T. 37, J. A. M. A. **100**:884 (March 25) 1933.

117. White, J. C.: Hop Hornbeam, J. Cutan. Dis. **14**:441, 1896.

118. Johnson, David W.: Dermatitis Due to Hyacinth Bulbs, Arch. Dermat. & Syph. **32**:289 (Aug.) 1935.

119. Northcote: Lancet **3**:1751, 1904.

120. Carpenter, C. C.: Dermatitis Produced by Hymolal Salts, Arch. Dermat. & Syph. **30**:517 (Oct.) 1934.

121. Industrial Dermatoses Among Printers, Miscellany, J. A. M. A. **77**: 1760 (Nov. 26) 1921.

122. McCord, C. P., and Minster, D. K.: Pyrethrum Dermatitis, J. A. M. A. **77**:448 (Aug. 6) 1921.

Cutaneous Irritants	Comment
Insect powder (black flag) [123]	Vesicular, erythematous, papular, urticarial wheals on the dorsum of the right hand and on arms, neck, legs and body
	The active irritant is pyrethrum
Insecticides [8]	The large number of irritants in the following list makes the use of insecticides a dangerous procedure at times: arsenic, trioxide, asafetida, peruvian balsam, barium carbonate, benzine, potassium bicarbonate, borax (sodium borate), calcium carbide, calcium chloride, calcium cyanide, calcium hydroxide, camphor, caraway seeds, carbolic acid crystals, carbon disulfide, carbon tetrachloride, cedar oil, cinnamon, cloves, cobalt chloride, copper carbonate, copper sulfate, mercury bichloride, cresol, creolin, creosote, crude tar, formaldehyde, gasoline, hellebore, iodoform, kerosene, linseed oil, mace, mustard, naphthalene, nutmeg, oils of anise, bergamot, cedar, citronella, eucalyptus, laurel, lemon grass, rape, sessamum and wintergreen, olive oil, orris, paradichlorobenzene, pepper (black or cayenne) petrol, poppy-seed oil, potassium arsenate, potassium bicarbonate, potassium cyanide, potassium fluoride, pyrethrum, sodium arsenate, sodium benzoate, sodium carbonate, sodium cyanide, soft soap, strychnine, sulfur flowers, sulfuric acid, tartaric acid, tobacco, Tonquin beans, turpentine
Iodine	Used as a local application
Iodoform	Redness, papules, vesicles and bullae
(White, J. C.,[3] p. 161)	Iodoform is used on the skin
Ipecac	Erythema, papules, vesicles and pustules
(White, J. C.,[3] p. 122)	
Ivy (common) (Hedera helix) [124]	Acrid juice is the irritant
	Wet leaves are more irritating than dry leaves
Jaborandi	The powder irritates by prolonged contact
(White, J. C.,[3] p. 125)	
Jacareuba [4]	Used in construction, carpentry and furniture
Jack-in-the-Pulpit	The fresh leaves and roots are irritating
(White, J. C.,[3] p. 73)	
Jamestown weed	Edema of the eyelids
(White, J. C.,[3] p. 132)	Medicinal uses
Japanese lacquer	
(White, J. C.,[3] p. 154)	
Jarrah wood [4]	Used in construction, cabinet work and paving blocks
Jute [125]	Reaction on the hands and forearms
	The irritant is the mineral oil used for softening the jute
Kabilene [126]	Used in dyeing a waist
Kapok [9]	
Karri [4]	Used in street paving, rafters, floors and bridges
Kerosene	
Kingwood [4]	Used in cabinet work and panels
Kleenex (tinted)	
Kotite (resin, beeswax, paraffin)	Used for coating the inside of beer barrels to prevent deterioration
Kwini mango [4]	
Label paper [127]	The irritant is a red dye
Laburnum [4]	Used in turnery and inlay and cabinet work
Lace	
Lace making and dyeing	Dyers suffer from the acid handled
(White, R. P.,[2] p. 268)	
Lacquer [128]	Used in Hawaiian pineapple factories and on lacquer canes
Lacquer shade (lamp)	
Lacquer tree	Gardeners are in contact with the tree and repot the plant

123. Sulzberger, Marion B., and Weinberg, C. B.: Dermatitis Due to Insect Powder, J. A. M. A. **95**:111 (July 12) 1930.

124. Munro, W. J.: A Case of Dermatitis Venenata Arising from a Rare Cause, Australia M. Gaz. **19**:25 (Jan. 20) 1900.

125. Curjel, D. F., and Acton, H. W.: Jute Dermatitis, Indian J. M. Research **12**:257 (Oct.) 1924; abstr., J. A. M. A. **84**:1081 (April 4) 1925.

126. Hudelo and Dumet: Dermatitis from a Waist Dyed with "Kabeline," Bull. Soc. franç. de dermat. et syph. **29**:92, 1922.

127. Rowell, H. G.: Dermatitis Venenata Caused by Colored Paper, Arch. Dermat. & Syph. **7**:603 (May) 1923.

128. Wayson, J. T.: Lacquer Dermatitis or Dermatosis Industrialis (Papulovesicular Lacquer), Arch. Dermat. & Syph. **8**:77 (July) 1923. Pusey, W. A.: Lacquer Dermatitis, ibid. **7**:91 (Jan.) 1923.

Cutaneous Irritants	Comment
La gerardine [129]	Reaction on the face and neck
	A hair-waving preparation, supposed to produce "natural" waves
Lampblack [130]	
Lancewood [4]	
Lanolin (hydrous wool fat U. S. P.) [42]	Lanolin is now found on nearly every toilet table
Larkspur	Redness and vesicles
(White, J. C.,[3] p. 119)	The tincture is used for destroying lice
Lash-lure [131]	Reaction on the eyelids
	The preparation is used as an eyelash and eyebrow dye
	The active irritants are an aniline derivative and magnesium
Lawson's cypress [4]	Used in casket, coffins, sashes, doors and blinds
Lead arsenate	
Lead salts	
Leadwood [4]	
Leatherwood [132]	
Leek	Redness and vesicles
(White, J. C.,[3] p. 102)	
Lemon juice [133]	Erythematous vesicular reaction on the hands and forearms
	The essential oil in the rind sets up a dermatitis
	Limonene is the active irritant
	Storing of lemons caused an attack
Lettuce [134]	Erythematous, papular and vesicular reaction on the hands and forearms in a salad maker
Lignum nephriticum [4]	Used in drinking cups and fountains
Lignum vitae [4]	Used in bearings or brushing blocks, pulley sheaves, bowling balls and brush backs
Lime	The hands of masons are affected
(White, J. C.,[3] p. 158)	
Linen [42]	
Linseed [135]	Red maculopapular lesions and follicular papules on the dorsa of the hands, the flexor surfaces of the forearms and the anterior part of the thighs
	The condition occurs in linseed oil crushers
	Residue of the cake is the irritant
	Pure linseed does not contain this irritant
Linseed oil	Irritation from sharp points on seeds in the linseed oils, parasites, oils of mustard and rape and filter mats
Lip-stick [136]	Reaction on the mucous membranes of the lips
	The active irritant is either eosin or rhodamine
Liquid arvon [137]	Reaction on the scalp and face
Contains:	
arsenic	
aconite	
carbolic acid (phenol U. S. P.)	
prussic acid (hydrocyanic acid U. S. P.)	
mercury bichloride	
strychnine	
Listerine	Reaction on the face and neck
	The preparation is used on the scalp
Lyddite (trinitrophenol)	
Lye (washerwomen's dermatitis)	
Lysol (saponated solution of cresol U. S. P.)	

129. Hollander, Lester: Dermatitis Produced by La Garardine, J. A. M. A. **101**:259 (July 22) 1933.

130. Dermatitis Due to Lampblack, Queries and Minor Notes, J. A. M. A. **68**:799 (March 10) 1917.

131. Greenbaum, Sigmund S.: Dermatoconjunctivitis Due to Lash-Lure, an Eyelash and Eyebrow Dye, J. A. M. A. **101**:363 (July 29) 1933.

132. Suchier: München. med. Wchnschr. **75**:570 (March 30) 1928.

133. Fanburg, S. V., and Kaufman, J. G.: Eczema Due to Lemon Peel, J. A. M. A. **97**:390 (Aug. 8) 1931.

134. Rinkel, Herbert J., and Balyeat, Ray M.: Occupational Dermatitis Due to Lettuce, J. A. M. A. **98**:137 (Jan. 9) 1932.

135. Barnes, M. H.: Linseed Dermatitis, J. Indust. Hyg. **13**:49 (Feb.) 1931.

136. Mayer, R. L.: Cosmetics: Their Injurious Effects, Med. Klin. **26**:1619 (Oct. 31) 1930.

137. Liquid Arvon, Report of the Bureau of Investigation, J. A. M. A. **102**: 860 (March 17) 1934.

Cutaneous Irritants	Comment
Macassar wood [4]	Used in inlay, sculptures, carvings, panels and veneer
Mah jong sets	
Mahogany [4]	Used in cabinet work, furniture and interior trims
Manchineel	Vesicles
(White, J. C.,[2] p. 96; Senear [4])	The branches contain a milky juice which irritates
	Used in wainscoting, cabinet making and tables
Mandrake	Reaction on the eyelids
(White, J. C.,[2] p. 76)	The powder of the root is irritating
Mango [4]	Fruit
Mansonia wood [138]	A case of dermatitis venenata due to mansonia wood has been reported
	The wood is used in the wood-working industry
Manures, artificial	Reaction in the armpits and bends of the elbows of persons working in factories
	The irritant is calcium superphosphate
Maotamea [4]	
Margarine	Reaction on the navel and the middle of the abdomen when the substance is carried in cups against the body
Marigold (legion of honor)	
Marking nut [4]	Seeds furnish oil
Mason work [139]	Reaction on the forearms, upper portions of the arms and axillae
	The irritation is due to lime powders, cement, plasters and concretes
Massaranduba [4]	Used in heavy construction, furniture, piles and submerged work
Masterwort	Vesicles
(White, J. C.,[2] p. 136)	The leaves are irritating
Matches [140]	Mild erythema to oozing on parts in contact with matches
Matches, safety	Reaction on the pocket area in men; on the fingers and conjunctiva in women
	The irritant is sesquisulfide, present on the surface of the box on which matches are struck
Matches, safety [141]	Reaction on the face, fingers and neck and also on the thighs in men, due to carrying or handling of safety matches
Mayweed	Vesicles
	The juice is irritating
Meadow grass	Linear vesicles
(Corson;[142] Schlammadinger [143])	
Meadow saffron	Redness
(White, J. C.,[2] p. 110)	Fresh corms are irritating
Melinite (trinitrophenol)	
Menstrual pads	Reaction in the pubic region
	Dermatitis from a rubber belt
Mercury	Used on the skin in the form of ointments, lotions, baths and fumigation
Mercurial ointment	
Ammoniated mercury ointment	A powerful caustic aqueous solution of 1 grain (0.065 Gm.) to the ounce (28.34 Gm.) generally causes no irritation
Solution of mercuric nitrate	
Solution of mercury bichloride	
	Surgeons who handle dressings and attendants may have reaction
Metal polish [144]	Reaction on the hands and forearms
Methylheptine carbonate [145]	Present in lip-stick
Metol (Methyl-aminocresol-sulfate)	Used by photographers
(White, R. P.,[2] p. 295)	The pure form is said by Herman to be innocuous to the skin

138. Honer, Sibyl: A Case of Dermatitis Venenata Due to Mansonia Wood (Sterculiacea Altissima), Brit. J. Dermat. **98**:26 (Jan.) 1936.

139. Artom, Mario: The Eczema of Masons, Lavaro **12**:225 (Dec.) 1921.

140. Wilson, D. J.: Match Dermatitis: Report of Unusual Case, Nebraska M. J. **18**:183 (May) 1933.

141. Rasch, C.: Match Box Dermatitis and Conjunctivitis, Ugesk. f. læger **83**: 1119 (Aug. 25) 1921.

142. Corson, Edward F.: Meadow Grass Dermatitis, Arch. Dermat. & Syph. **32**:616 (Oct.) 1935.

143. Schlammadinger, Josef: Skin Diseases Due to Plants with Particular Reference to Meadow Dermatitis, Dermat. Ztschr. **67**:324 (Oct.) 1933.

144. Dermatitis from Metal Polish, Queries and Minor Notes, J. A. M. A. **99**: 245 (July 16) 1932.

145. Hoffman, M. J., and Peters, J.: Dermatitis, Due to Facial Cream, Caused by Methyl Heptine Carbonate, J. A. M. A. **104**:1072 (March 30) 1935.

Cutaneous Irritants	Comment
Metol [119] (methyl-aminocresol sulfate)	Reaction on the fingers Used as a developer
Mexican bird weed seed [146]	
Mezereon	
Mica (aluminum silicate)	
Milfoil or nosebleed (Achillea millefolium) [147]	A farmer had irritation from milfoil when it was mixed with sheaves of barley; this plant may cause an eruption in bathers
Milking [148]	Reaction caused by handling the udders of cows after they had walked among dew-laden flowers, probably the white or lilac umbels of the wild Primula farinosa
Mizar [149]	Violent dermatitis on parts where the preparation is rubbed and bandaged A nostrum, a supposed remedy for rheumatism; red pepper is the active ingredient
Moahwood [4]	Used in ship-building, railroad ties, flooring and tools
Mohair (Coca; [8] Rowe and Rogers [150])	
Molucca ebony [4]	Used in turnery and inlay
Monk's-hood (White, J. C.,[3] p. 117)	Redness and vesicles The plant is worked for aconite
Moosewood (White, J. C.,[3] p. 133)	Redness and vesicles The fresh bark is irritating
Morphine and its esters [151]	Reaction on the arms and hands of persons working in a chemical factory in Germany after they had washed some cloths through which morphine had been filtered
Mossy stonecrop (White, J. C.,[3] p. 90)	Redness and vesicles on the hands The plant is used for edgings in flower gardens; the juice is irritating to gardeners
Moth-mullen (plant) [152]	Reaction on the face and left wrist Moth-mullen is used in homes as a decorative plant; the leaves are often placed between clothing to keep moths away
Moule wood [4]	Used in hardwood and interior trim
Mountain cedarwood [4]	Used in pencil making
Mouth washes	
Muirapanga [4]	Used in furniture, flooring, ship construction and bridge timbers
Mullen (White, J. C.,[3] p. 101)	Roadside weed covered with thick hairs which are irritating to the skin
Multigraph ink [153]	Redness, vesicles and pustules on the right hand of workers with multigraph machine Green inks on stocks and bonds and rotogravure ink may cause dermatitis
Mundic (iron pyrites diarsenide)	Dust is capable of giving rise to dermatitis
Muriatic acid (hydrochloric acid U. S. P.) (White, J. C.,[3] p. 156)	Generalized erythema or a mild follicular inflammation Used in weak solutions, as in baths and fomentations
Mustard (White, J. C.,[3] p. 91)	Volatile oil of mustard is a powerful irritant
Mustard gas	
Naphtha	
Nasal spray [154]	Reaction on the upper lip and side of the nostrils due to ephedrine in oil

146. French, S. W.: Case of Skin Sensitivity to Parthenium Hysterophorus, Mil. Surgeon **66**:673 (May) 1930.

147. Low, R. Cranston: Skin Sensitiveness to Non-Bacterial Proteins and Toxins, Brit. J. Dermat. **36**:292 (July) 1924.

148. Sharpe, H. A.: Primula Dermatitis, J. A. M. A. **59**:2148 (Dec. 14) 1912.

149. Mizar Again, Report of the Bureau of Investigation, J. A. M. A. **93**: 1240 (Oct. 19) 1929.

150. Rowe, A. H., and Rogers, H.: Allergic Dermatitis: Case Due to Mohair, California & West. Med. **23**:1589 (Dec.) 1925; abstr., J. A. M. A. **86**:306 (Jan. 23) 1926.

151. Levin: Med. Klin. **4**:1633, 1908.

152. Steiner-Wourlisch, A.: Unusual Cases of Dermatitis Venenata, Klin. Wchnschr. **9**:205 (Feb. 1) 1930.

153. Eczema from Multigraph Ink, Queries and Minor Notes, J. A. M. A. **93**:55 (July 6) 1929.

154. Scheer, M.: A Case of Dermatitis Venenata Due to Ephedrine, Arch. Dermat. & Syph. **20**:641 (Nov.) 1929.

Cutaneous Irritants	Comment
Neko soap [155]	Reaction on the hands and forearms
	The active irritant is potassium mercuric iodide
Nerium oleander	
Newspaper [42]	Brown section of Sunday paper; daily paper
Nickel [156]	Reaction on the temples and ears, left wrist, and bridge of the nose and lateral aspects of the thighs
	White gold, copper and nickel salts are liberated when nickel is worn; irritation occurs most often during hot weather; it may be due to spectacle frames, wrist watch, garter clasps
Nickel baths [157]	Reaction on the face, neck and arms of a girl doing galvanizing
Nickel-plating [158]	The literature has been brought up to date so far as nickel eczema produced by plated objects and alloys is concerned
Nickel-plating	Reaction on the hands and forearms
(White, R. P.,[3] p. 290; Foster and Ball [158])	Irritants: nickel sulfate, potassium cyanide, benzine, petroleum, lime and strong sodas used for cleaning metals
Night-blooming cereus	Vesicles and pustules
(White, J. C.,[3] p. 78)	The plant is cultivated for its showy and evanescent bloom
Nitric acid	
(White, J. C.,[3] p. 156)	
Nitrosophenol [159]	
Norway spruce	Redness and papules
(White, J. C.,[3] p. 89)	The exuding resin is called burgundy pitch and when used in the form of a plaster applied to the skin is irritating
Novocain (procaine hydrochloride U. S. P.)	Reaction on the fingers and hands of dentists
Nupercaine [160]	Vesicular bullous reaction on the anal region
	Nupercaine is used in the treatment of hemorrhoids; a new local anesthetic
Oak [161]	
Ochre	Used as dye for curtains
Ocular work [162]	Reaction on the thumb, index finger and middle fingers of oculist
Oil (cutting)	Mechanical abrasions
Oil of bergamot [163]	Erythema, urticarial wheals and vesicles at the point of application; reaction often present on the neck, chest, back and shoulders
	The oil is used in eau de cologne and toilet waters
	Irritation follows long exposure to the sunlight; dermatitis is more severe in blonds (natural), but pigmentation is more severe in brunettes
Oil of cassia	Redness and vesicles on the hands, face and abdomen
(White, R. P.,[3] p. 442)	
Oil of citronella [164]	Used to kill mosquitoes

155. Dermatitis from Potassium Mercuric Iodide Soap—Induration from Mercuric Salicylate Injection, Queries and Minor Notes, J. A. M. A. **97**:1644 (Nov. 28) 1931.

156. Lain, Everett S.: Nickel Dermatitis: A New Source, J. A. M. A. **96**: 771 (March 7) 1931.

157. Fuhs: Nickel Itch, Zentralbl. f. Haut- u. Geschlechtskr. **24**:750, 1927.

158. Foster, Paul D., and Ball, Franklin I.: Sources of Nickel Eczema, Arch. Dermat. & Syph. **31**:461 (April) 1935.

159. Osborne, E. D., and Putnam, E. D.: Industrial Dermatoses, J. A. M. A. **99**:972 (Sept. 17) 1932.

160. Fowlkes, Richard W.: Dermatitis Due to Nupercaine, J. A. M. A. **100**: 1171 (April 15) 1933. Fanburg, S. J.: Dermatitis Due to Nupercaine, ibid. **101**:30 (July 1) 1933.

161. Spillmann, L.: Artificial Dermatitis Due to the Action of Oak (Quercus Rober), Bull. Soc. franç. de dermat. et syph. **28**:33, 1921.

162. Spillmann, L., and Mougolle: Painful Occupational Keratosis of the Nails, Bull. Soc. franç. de dermat. et syph. **32**:49 (Jan.) 1925.

163. Lane, J. E., and Strauss, M. J.: Toilet Water Dermatitis, with Especial Reference to "Berlock" Dermatitis, J. A. M. A. **95**:717 (Sept. 6) 1930.

164. Lane, C. G.: Dermatitis Caused by Oil of Citronella, Arch Dermat & Syph. **5**:589 (May) 1922.

Cutaneous Irritants	Comment
Oil of lavender	Pigmentation Oil of lavender is used and acts in the same way as oil of bergamot
Oil of turpentine (White, J. C.,[2] p. 146)	The vapor is more stimulating than direct contact
Oilcloth [165]	
Oleander (Nerium oleander)	Redness and vesicles An ornamental tree, the oil from which is irritating
Oleic acid [166]	May affect stenographers handling stencil sheets
Olive oil (White, R. P.,[2] p. 274)	Prolonged contact is necessary to produce a reaction
Olive wood [4]	Used in inlays and ornaments
Onion (White, J. C.,[2] p. 102)	Redness and vesicles
Orange [167]	
Orange bitter	Erythema and papular vesicles on the left hand, which holds fruit while one is cutting it The fruit is used in the manufacture of marmalade
Orange peel, oil of [168]	Erythematous papular, vesicular reaction on the hands of employees making oils of orange
Oriental cashew or indian marking nut	Vesicles and bullae The nut stains the skin black
Orris [8]	A frequent factor in infantile eczema Used in cosmetics, face and talcum powder, tooth powders and pastes, shaving powders, sachets, face packs, astringent packs, cleansing powder and creams, scented soaps, dry shampoo, adhesive plaster, sweetmeats and pastries
Orthoform	Vesicles and bullae
Osage orange [169]	
Oxalic acid (White, R. P.,[2] pp. 129, 284 and 286)	In polishing patent leather
Ox-eyed daisy (White, J. C.,[2] p. 88)	Papular and vesicular reaction on the fingers A common weed
Oxygenaire (soda lime) [170]	
Paint solvents [171]	Turpentine and naphtha are the irritants
Paraffin, boiling of [172]	Reaction on the hands from dipping cardboard into a kettle
Paranitrosodimethylanilene [159]	Chemical used as an accelerator for curing rubber
Paraphenylenediamine (ursol)	Reaction on the forehead, eyes, face and neck; repeated applications or wearing causes dermatitis in any person
Partridge wood [4]	Used in heavy construction
Pasque flower (White, J. C.,[2] p. 118)	Redness and vesicles
Patent cleaners	
Patent soap powders	
Peaches, fur on [173]	Erythema and papules on the face, neck, forearms and cubital fossa of workers in the fruit-canning industry
Peanut oil [8]	
Pear [4]	Used in mathematical and drawing instruments and rulers
Peas [1]	

165. Dreyer: Oilcloth Dermatitis, München. med. Wchnschr. **68**:1000, 1921.

166. Hailey, W. H.: Dermatitis from Oleic Acid, Arch. Dermat. & Syph. **8**:530 (Oct.) 1923.

167. Scott, J. A.: Case of Orange Dermatitis, Brit. J. Dermat. **46**:378 (Aug.-Sept.) 1934.

168. Kober, G. M., and Hanson, W. C.: Diseases of Occupation, Philadelphia, P. Blakiston's Son & Co., 1922, p. 368.

169. Schur, Albert: Dermatitis Venenata Due to Osage Orange, Arch. Dermat. & Syph. **26**:312 (Aug.) 1932.

170. Gandy, Truett: Dermatitis from Oxygenaire: Report of a Case, Arch. Dermat. & Syph. **27**:951 (June) 1933.

171. Turner, J. A.: Acute Dermatitis Among Painters Employed in Industrial Plant, J. Indust. Hyg. **7**:293 (July) 1925.

172. Teleky, L., and Brezina: Abstr., J. Indust. Hyg. **5**:35 (May) 1923.

173. A Survey of Women in Industry, Foreign letter (Australia), J. A. M. A. **93**:931 (Sept. 21) 1929.

Cutaneous Irritants	Comment
Pellitory ..... (White, J. C.,[3] p. 78)	Root used in medicine
Pen holders	
Penicillium	
Pepper, black and white..... (White, J. C.,[3] p. 117)	Redness and vesicles The active principle is chiefly pepperine
Perfume	
Perfume [174]	Women use it on exposed parts of the body; men use it on the face after shaving The oil of bergamot it contains is the active irritant Three factors seem essential: (1) sensitivity of the person; (2) ingredients of the perfume; (3) natural summer sunlight
Perfumes, synthetic violet [175].....	
Peroba [4]	Used in ox yokes, house construction, boat building and piles
Peroba amarella [4]	Used in furniture, cabinet making, flooring and turnery
Peroba perdu [4]	Used in construction, furniture and flooring
Petrolatum	Used as a lubricant
Petroleum ..... (White, J. C.,[3] p. 151)	It is doubtful whether the crude oil irritates; there is more irritation during hot weather; the reaction depends on paraffin products
Petroleum, crude [176]	Vesicles, bullae and ulceration on the extremities Petroleum is more prone to cause a reaction when the skin is wet
Petroleum naphthas	Erythema and vesicles
Benzene from coal Benzene from paraffin and other like distillates	These products dry and contract the skin
Phenol and its derivatives.....	
Phenylendiamine [177]	Phenylendiamine dermatitis may be delayed from twenty-four to forty-eight hours Four per cent of normal persons show idiosyncrasy
Phenylhydrazine hydrochloride [178]...	Erythema and vesicles on the hands and fingers of a student using the chemical Reaction resulted from wearing clothing on which a solution of phenylhydrazine had been spilled
Phosphorus match box.....	
"Photogravure" section of the Sunday newspaper [179]	The active irritant is paranitraniline red, the color used in the ink
Photography (metol [methylaminocresol sulfate])	Reaction on the hand nearest the ruby lamp Irritants used: pyrogallic acid, metal, hydroquinone, amidol, robinol Metol gives the epidermis a polished appearance Pure metol is said not to be irritating
Picric acid (trinitrophenol U. S. P.) (White, R. P.,[2] p. 175)	Erythema of the face, hands and arms; workers have a light yellow hue on the skin More serious irritation is caused by solution than by dust Picric acid is used as a wet dressing in medicine Ammonia removes the stains from the skin
Pictorial papers (rotogravure) [179]...	Reaction on the face and eyelids The irritant is paranitraline red
Pilocarpine powder ..... (White, J. C.,[3] p. 126)	Irritation from prolonged contact
Pimento, oil..... (White, J. C.,[3] p. 112-113)	
Pistachio meal (ground nuts) [3].....	Used in the manufacture of soap
Pix liquida (tar)..... (White, J. C.,[3] p. 112-113)	

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Plants:

Irritating Plants of the United States [180]

Scientific Name	Common Name
Abies excelsa	Norway spruce
Aconitum napellus	Aconite
Actaea alba (L) Mill.	White baneberry
Actaea spicata	Baneberry
Agave americana	Century plant
Ailanthus glandulosa	Tree of heaven
Alismo plantago	Water-plantain
Allium sativum	Garlic
Ambrosia artemisiifolia	Common ragweed
Ambrosia psilostachya	Western ragweed
Anemone patens	Pasque flower
Anome quinquefolia L.	Wood anemone
Anthemis cotula L.	Dog fennel
Aralia spinosa L.	Southern prickly heat
Arctium lappa L.	Burdock
Arisaema triphyllum (L) Schott.	Indian turnip
Artemisia heterophylla Nutall	California mugwort
Asparagus officinalis L.	Asparagus
Bidens frondosa L.	Beggar ticks
Borago officinalis L.	Borage
Brassica alba (L) Boiss.	White mustard
Brassica nigra (L) Koch	Black mustard
Buxus sempervirens L.	Box tree
Cactus grandiflorus	Night-blooming cereus
Capsicum fastigiatum	Red pepper
Catalpa catalpa (L) Karst.	Catalpa tree
Caulophyllum thalictroides (L) Michx.	Blue cohosh
Ceanothus velutinus Dougl.	Sticky laurel
Chelidonium majus	Celandine
Chimaphila umbellata (L) Nutt.	Pipsissewa
Chrysanthemum leucanthemum L.	Ox-eye daisy
Chrysanthemum Parthenium (L) Pers.	Feverfew
Clematis virginica L.	Virgin's bower
Colchicum autumnale L.	Meadow saffron
Convallaria majalis L.	Lily of the valley
Cypripedium hirsutum Mill.	Yellow ladies' slipper
Cypripedium parviflorum Salisb.	Small yellow ladies' slipper
Cypripedium reginae Walt.	Showy ladies' slipper
Daphne mezereum L.	Mezerum
Datura stramonium	Jamestown weed
Daucus carota L.	Wild carrot
Dirca palustris L.	Leather-wood
Drosera rotundifolia L.	Sundew
Echium vulgare L.	Viper's bugloss
Erigeron canadensis L.	Butter-weed
Euphorbia antisyphilitica Zuec.	Candelilla
Euphorbia corollata L.	Flowering spurge
Euphorbia cyparissias L.	Cyprus spurge
Euphorbia helioscopia L.	Wart weed
Euphorbia ipecacuanhae L.	Ipecac spurge
Euphorbia lathyrus L.	Caper spurge
Euphorbia marginata Pursh.	Snow on the mountain
Fagopyrum fagopyrum (L) Karst.	Buckwheat
Fiscus carica L.	Fig
Gelsemium sempervirens (L) Ait. f.	Yellow jessamine
Ginkgo biloba L.	Ginkgo tree
Hedra helix L.	Ivy
Helenium autumnale L.	Sneezewood
Helianthus annuus L.	Sunflower
Heracleum lanatum Michx.	Cow parsnip
Hibiscus esculentus L.	Okra
Hippomane Mancinel la L.	Manchineel
Humulus lupulus L.	Hop
Iris florentina L.	Orris root
Iva xanhifolia Nutt.	Marsh elder
Juniperus virginiana L.	Red cedar
Laportea canadensis	Wood nettle
Lepidium sativum L.	Garden cress
Lilium longiflorum	Long-flowered white lily
Lilium superbum L.	Turk's cap lily
Linum usitatissimum L.	Common flax
Liquidambar styraciflua L.	Sweet gum
Lobelia inflata L.	Lobelia
Narcissus pseudo-narcissus L.	Daffodil
Nerium oleander L.	Oleander
Oenothera biennis L.	Evening primrose
Oxdendrum arboreum DC.	Sorrell tree
Pastinaca sativa L.	Parsnip

180. Weber.[1] The original list of irritating plants in the United States was furnished to Dr. William Allen Pusey by the Bureau of Plant Industry of the Department of Agriculture in March 1923. I have checked these plants from many sources, and I believe that the list is accurate.

Scientific Name	Common Name
Phacelia infundibuliformia Torr.	
Phleum pratense L.	Timothy
Phtolacça decandra L.	Pokewood
Picea canadensis (Mill)BSP.	White spruce
Podophyllum peltatum L.	May-apple
Polygonum acre HBK.	Water smartweed
Polygonum hydropiper L.	Smartweed
Polygonum punctata Ell.	Dolled smartweed
Populus candicans Ait.	Balm of Gilead
Primula farinosa L.	Bird's-eye primula
Psoralea esculenta Pursh.	Pomme de prairie
Puccinia graminus Pers.	
Ranunculus californicus	
Ranunculus sceratus L.	Cursed crowfoot
Rhus toxicodendron L.	Poison ivy
Rhus vernix L.	Poison sumac
Roripa armoracia (L) Hitchcock.	Horseradish
Ruta graveolens L.	Garden rue
Sanguinaria canadensis L.	Blood root
Sassafras varifolium (Salisb.) Katzl.	Sassafras
Sedum acre L.	Mossy stonecrop
Sicyos angulatus L.	Bur cucumber
Sisymbrium officinale (L) Scop.	Hedge mustard
Stillingia sylvatica L.	Queen's delight
Symplocarpus foetidus (L) Nutt.	Skunk cabbage
Syringa vulgaris L.	Lilac
Thuja occidentalis L.	Arbor vitae
Toxylon pomiferum Raf.	Osage orange
Tropoleum majus L.	Nasturtium
Urtica chamaedryoides Pursh.	Nettle
Urtica dicia L.	Stinging nettle
Urtica gracilis Lit.	Slender nettle
Urtica urens L.	Small nettle
Veratrum viride L.	American hellebore
Verbascum thansus L.	Common mullein

Tropical Plants Producing Dermatitis [70]

Genus	Species	Common Name
Anacardiaceae	Comocladia dentata, Jacquin.	Guao
	Comocladia glabra, Sprengel, variety acuminata	Guao
	Comocladia hollokii, Britton	Guao
	Comocladia grandidentata, Britton	Guao
	Comocladia Ehrenbergii, Engler	Guao
	Comocladia parvifolia, Britton	Guao
	Comocladia cordata, Britton.	Guao
	Comocladia pubescens, Engler	Guao
	Comocladia jamaicencis, Britton	Guao
	Comocladia velutina, Britton	Guao
	Comocladia pilosa, Britton	Guao
	Comocladia ondulata, Urban	Guao
	Comocladia intermedia, Wright	Guao
	Comocladia platyphilla, Richard	Guao
	Comocladia dominguensis, Britton	Guao
	Comocladia dodonaeae, Britton	Guao
	Comocladia acuminata, Britton	Guao
	Metropium browneii, Urban, or M. toxiferum, Linné	Guao de costa
	Anacardium occidentale, Linné.	Marañón
	Rhus venosa, Grisebach.	
Rhus metropium, Linné.		
Leguminosae	Mucuna pruriens, DeCandolle, or Dolichos pruriens, Linné, or Stizolobium pruriens, Medicus	Pica-pica, cowhage, cowitch
Euphorbiceae	Platygyne pruriens, Baillon or Platygyne urens, Linné	Pringamoza
	Tragia volubilis, Linné.	Pringamoza morada
	Jatropha urens, Linné.	Chaya
	Hura crepitans, Linné.	Salvadera
	Euphorbia lactea, Haworth.	Cardon
	Jatropha curcas, Linné.	Poñón de botija
	Hippomane mancinella, Linné.	Manzanillo
	Acidoton urens, Sw.E.	
	Acidoton microphyllus, Urban.	
Urticaeae	Fleurya umbellata, Weddell.	Ortiguilla
	Fleurya aestuans, Guadichard-Beupré.	
	Urera baccifera, Guadichard-Beupré.	Chichicate
	Urera dominguensis, Urban.	
Malpighiaceae	Malpighia urens, Linné	
Malvaceae	Malchra urens, Poiteau.	Malva Santo Domingo
Lytrareae	Cuphea urens, Kaehne.	
Araceae	Phylodendrum consanguineum, Schott.	
Apocinaceae	Tabernaemontana citrifolia, Linné.	Pegojo

Cutaneous Irritants	Comment
Plaster	
Poison ivy	
Poison oak	
Poison sumac [4]	
Poison wood [4]	Used in furniture and inlays
Pollen	
Poplar [4]	Used as lumber, for paper-pulp and in construction, interior finishing and boat building
Porcelain workers [181]	Possible irritants: lime used in the glaze, chrome salts used in coloring some porcelain, mechanical action of chemically inert dusts on the skin plus action of excessive heat of oven, and too harsh detergents
Portuguese man-of-war (White, J. C.,[3] p. 189; Crutchfield[182])	Linear lesions, vesicles and hemorrhagic lesions
Prickly elder (White, J. C.,[3] p. 74)	The green bark acts as an irritant on the hands of the collector
Primrose	
Primula farinose	Grows wild
Primula obconica [183]	The juice of the plant is irritating
Primula cartusoides	All domestic varieties
Primula sieboldii	
Primula sinensis	
Prince's pine (White, J. C.,[3] p. 93)	Redness and vesicles
Printing [184]	Irritants used: turpentine, benzine and lye Removing the ink stains from the hands with a stiff brush and sand is irritating; sawdust should be substituted for sand and gentler friction used
Procaine [185]	Dermatitis on eyelids from drops containing procaine
Procaine hydrochloride [185]	Reactions on the upper and lower eyelids, the sides of the nose and the upper part of the cheeks
Prunes, sorting of [186]	Probably irritation from the molds
Pumpherston (a shale oil) (White, R. P.,[2] p. 200)	Folliculitis of the hands and forearms Hemp being oiled with shale oil and pressed into cans
Purple wood [4]	Used in billiard tables and cues, inlay and cabinet work
Pyrethrum	Papular and vesicular reaction Used as an insecticide
Pyrogallic acid (pyrogallol U. S. P.) (White, R. P.,[2] p. 294)	Reaction around the nails and between the fingers of photographers using the substance as a developer; the stain is objectionable
Queen's root (White, J. C.,[3] p. 98)	Redness and edema of the hands The juice of the green root is irritating
Queensland maple [4]	Used in general building and cabinet work and in making rifles and wheels
Quicklime (lime U. S. P.) (White, J. C.,[3] p. 158)	Mild irritation on the hands of masons
Quinine [187]	Generalized and localized reaction on the face caused by quinine in an after-shaving lotion
Quinine sulfate (White, J. C.,[3] p. 124)	Erythema, vesicles, pustules and crusts on the hands, forearms, face and genitals; also a generalized reaction in men employed in boiling the bark, converting the quinine into the sulfate and placing the sulfate in the bath

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Cutaneous Irritants	Comment
Ragweed [188]	Erythematous, papular and vesicular reaction on the feet, shins, calves, flexor surfaces of the arms and upper portion of the chest; eyelids swollen and reddened Reaction occurs between the latter part of August and the end of September
Ragweed (Ambrosiaceae) [189]	Reaction on exposed surfaces in farmers and other persons in rural districts of the agricultural belt of the Middle West
Rattan	
Rayon	
Red bean [4]	Used in furniture, cabinet making and paneling
Red pepper (White, J. C.,[3] p. 131)	Redness and vesicles Used for table purposes and pharmaceutically, as in plasters
Redwood [191]	
Reeds	
Rengas [4]	Used in ornamental work and fine furniture
Resin [190]	
Resin (propolis) [191]	Propolis is the gluelike substance produced by bees to cement various portions of the hive; it causes a dermatitis
Resorcinol [192]	
Resorcinol [193] (metadihydroxybenzene)	Reaction on the anal region from anusol suppositories
Rhus family	
Rhus diversiloba (poison oak)	
Rhus radicans (poison vine)	
Rhus toxicodendron	The active principle is toxicodendrol (poison ivy)
Rhus vernicifera (White, J. C.,[3] p. 52)	
Rhus vernix (White, J. C.,[3] p. 32)	
Rice [194]	
Rouge (quick rouge) [195]	Reaction on the forearms and backs of the hands The irritant is ferric oxide Quick rouge is used for polishing metals and as a pigment for paints, silver polishes and burnishers; the finest crimson rouge is used for polishing gold coarser rouge is used for burnishing brass and copper
Rouge paste (White, R. P.,[2] p. 103)	Reaction of the cheeks The ingredient that probably caused irritation was powdered pumice
Rubber, artificial	
Rubber (condom) [196]	
Rubber gloves [159]	Mild erythema to bullous lesions on the hands and wrists of lineman who wore rubber gloves while working on high voltage lines Irritation caused by tetramethylthiuramdisulfide
Rubber industry (the making of tires, rubber shoes and surgical gloves) (White, R. P.,[2] p. 252)	Fissures and scaling vesicles on the hands, forearms and various parts of the body Irritants: Urotropine (compounders, mixers and calenderers), formic acid, hexanitrodiphenylamine (hex) used in a rubber tire factory, aniline oil and sulfur chlorides

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192. Taylor, J.: J. Cutan. Dis. **13**:169, 1895.

193. Mitchell James H.: Resorcin Anal Dermatitis Due to Resorcin in Anusol Suppositories, J. A. M. A. **101**:1067 (Sept. 30) 1933.

194. Alderson, H. E., and Rawlins, A. G.: Rice Worker's Dermatitis, California & West. Med. **23**:42 (Aug.) 1925.

195. Hall, A. C.: Brit. J. Dermat. **16**:121, 1902.

196. Rattner, H.: Dermatitis of the Penis from Rubber, J. A. M. A. **105**:1189 (Oct. 12) 1935.

Cutaneous Irritants	Comment
Rulers	
Sabicu [4]	Used in furniture, interior trimming and turnery
Salad making [197]	Reaction on hands and forearms and about the nose and throat from handling and eating lettuce
Salicylic acid [198]	Has a keratolytic action
Salt, common (sodium chloride), and its solutions [199]	Redness of skin of women working in brine establishments
	Salt in a weak solution may irritate if the horny layer is absent
Sand	Mechanical abrasions
Sand-box	Redness and vesicles
(White, J. C.,[3] p. 97)	The milky juice is irritating
Sand-box tree [4]	Used in furniture, cabinet work, interior trimming and veneer
Santo wood [4]	Used in cutlery handles, turnery and billiard cues
Sapo viridis	A violent irritant
(White, J. C.,[3] p. 115)	Used injudiciously in the treatment of dermatoses
Sassafras [200]	
Satin nut wood [4]	Used in furniture, paving blocks and shingles
Satinwood [201]	Macular, papular and vesicular reaction on exposed parts
	Satinwood is used as a trimming in the manufacture of furniture
Sawdust (wet)[202]	Reaction on the hands and forearms (the right hand being more affected than left) of a sweeper in a department store
Scheele's green	Ulcerations
(White, R. P.,[2] p. 146)	Contains 55% arsenic
Scratch brushing	Process consists of cleaning a piece of jewelry by means of a revolving brush; sour beer fell on the brush
Sea grape [4]	Used in furniture and cabinet work
Sealing wax	
Sensol	A new explosive; formula is secret
Shampoo (dry)[203]	Reaction on the interdigital webs of persons in the hairdressing trade
	Pyridine and potassium carbonate are the irritants
Sheep wool [3]	
Sheepskins (dyed)[204]	Reaction on the arms and forearms of workers in a garment factory
Shirt (new black cotton)[205]	Erythema of parts that come in contact with the shirt
Shoe cleaners (white)[206]	Reactions on the feet
	Tinea should be excluded
	Cleaners contain whiting, French chalk, fuller's earth, zinc oxide, ultramarine blue, lithopone, turpentine, white wax, white soap, shellac, phenol, oxalic acid, alum, borax (sodium borate U. S. P.), milk, glycerin, benzine, ammonia, ethyl alcohol, methyl alcohol (wood), tragacanth, acacia, carbon tetrachloride, oil of bitter almonds, oil of citronella

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201. Satin Wood Dermatitis, Queries and Minor Notes, J. A. M. A. **98**:1932 (May 28) 1932.

202. Levin, Oscar L.: Sawdust Dermatitis, J. A. M. A. **100**:570 (Feb. 25) 1933.

203. Mumford, P. B.: Two Forms of Dermatitis Due to the Use of Methylated Spirit Externally, Brit. M. J. **2**:607 (Oct. 3) 1925.

204. Dermatitis from Handling Dyed Sheepskins, Queries and Minor Notes. J. A. M. A. **96**:461 (Feb. 7) 1931.

205. Jamieson: Boston M. & S. J. **1**:78, 1897.

206. White Shoe Cleaners, Queries and Minor Notes, J. A. M. A. **97**:557 (Aug. 22) 1931.

Cutaneous Irritants	Comment
Shoe dressings [207]	Reaction on the hands of leather dressers, shoe finishers and shoe shiners
	Dressings contain methyl alcohol, carbon disulfide, benzine, shellac, nigrosin (aniline black), logwood, turpentine, camphor, gum rubber, orthodichlorobenzene
Shoe leather [208]	
Shoe leather [209]	Reaction on the feet
	Irritant is either the free chromic acid or excessive amounts of water-soluble dyestuffs
Silicate wool [210]	Used for packing around cold storage apparatus, steam-pipes and boilers
Silk (real) [42]	
Silk and the silk industry [211]	Hazard greater for the silk worker than for the wearer
	Possible irritants: tin tetrachloride, formic acid, dyes, sodium silicate, barium salts, dextrin, glues, linseed oil, Japan wax, sodium toluneparasulfonchloro-amine, vegetable mucilages, liquid petrolatum, rubber solutions
Silver nitrate	Vesicles if the drug is rubbed violently into the skin
(White, J. C.,[3] p. 171)	
Silver sprucewood [4]	Used in airplane construction, boat building, oars and door and window sashes
Singapore mahogany [4]	Used in ornamental work and fine furniture
Skunk cabbage	Redness
(White, J. C.,[3] p. 74)	The dry root is irritating
Slub dyeing [212]	Papules on the knuckles, in the fold of the thumb and first finger and on the palmar surface of the wrist and forearm
	Roving dyed before the wool is spun into thread
Smartweed	Redness of the hands and face
(White, J. C.,[3] p. 117)	The juice irritates the collector
Snakewood [4]	Used in canes, umbrella handles and drumsticks
Soap (harsh) [213]	Mechanical abrasions
Soap (powders)	Grinders, weighers and packers are affected
Soapstone	Irritates when it penetrates the clothing
	Coarser varieties of soapstone are especially irritant
Soap, tincture of green [214]	
Soda soaps	Drying effect on the skin when the alkali is present in excessive amount
(White, J. C.,[3] p. 158)	
Sodium arsenate	
Sodium chloride (salt)	Irritating, especially when in powder or crystal form
(White, R. P.,[3] p. 267)	
Sodium hydroxide	
Sodium salicylate	
Soluble oil (olein)	A sulfonated product of castor oil, used as a mordant in the preparation of cotton fiber
(White, R. P.,[3] p. 314)	
Sorghum vulgare [215]	The irritant is either sorghum or a parasite; probably mechanical irritation is produced during the cutting of sorghum
South African boxwood [4]	Used in turnery, inlays, rulers and instruments
Spanish fly	Redness, vesicles and bullae
(White, J. C.,[3] p. 197)	

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211. Dermatitis in Silk Industry, Queries and Minor Notes, J. A. M. A. **103**:939 (Sept. 22) 1934.

212. Legge, T., in Annual Report of H. M. Chief Inspector of Factories, 1905.

213. Downing, J. G.: Industrial Dermatoses, J. Indust. Hyg. **17**:138 (July) 1935.

214. Johnson, David W.: Dermatitis Due to Tincture of Green Soap, Arch. Dermat. & Syph. **29**:104 (Jan.) 1934.

215. Hoffer, G.: Dermatitis in Sorghum Harvesters, J. A. M. A. **70**:1801 (June 8) 1918.

Cutaneous Irritants	Comment
Spanish jasmine [4]	Yields perfume
Spotted gum [4]	Used in ship and house building and cabinet work
Spruce	Redness, papules and pustules
(White, J. C.,[3] p. 89; Senear [4])	Used in interior work, joinery and paper pulp
Spun glass [102]	Vesicles and edema affecting the right hand
	Used for decorating a Christmas tree with "angel hair"
Stearic acid [216]	Reaction on the arms and face
	Used to soften rubber
Stocking (dyed)[217]	Bullae and edema affecting the legs
	Stockings dyed with erythrosin, eosin or aurin
Stocking finishes [218]	Reaction on the area of the feet covered by the socks
	The active irritant is the dye in certain stripes in rayon hose and the finishes, sulporicinol S, sulfonated castor oil, borax (sodium borate U. S. P.) and olive oil soap
Stone-acre	Reaction on the face and hands
(White, J. C.,[3] p. 119)	
Sugar	
Sulfur	Reaction on the backs of the hands and forearms
(White, R. P.,[2] p. 335)	Sodium sulfide is a highly active irritant; eruptions occur in jiggers; sulfur colors on yarns and cloths have to be washed to remove any adhering sodium sulfide, otherwise it gives trouble if material is handled or worn
Sulfur color solution	Reaction on the backs of the hands and forearms
(White, R. P.,[2] p. 335)	Stirring the boiling solution with a wooden paddle was sufficient exposure to cause irritation
Sulfonated oil [159]	Reaction on exposed parts
	Used in rayon plants
Sulfuric acid	Erythema and papules
(White, J. C.,[3] p. 155)	The diluted acid is used in the treatment of cutaneous diseases and in the arts
Sulfurous acid	Used in the treatment of pruritus
(White, J. C., [3] p. 155)	
Sumac	A vegetable tannin causes a definite dermatitis
(White, R. P.,[2] p. 300)	
Sunday and daily newspaper [179]	Reaction on the hands and face
Sundew	Vesicles
(White, J. C.,[3] p. 92)	
Suppositories [219]	Reaction on genitals from quinine contained in contraceptive suppositories
Surinam greenheart [4]	Used in fishing rods, turnery, vehicles and cabinet work
Surinam snakewood [4]	Used in general construction, fence posts and fuel
Sweets, packing of [220]	Sugar is the irritant
Tagayasan nut tree [4]	
Tallow	Reaction on the navel and middle of the abdomen when tallow is carried in cups against the body
(White, R. P.,[2] p. 273)	
Tannic acid	
(White, J. C.,[3] p. 95)	
Tar	
(White, J. C.,[3] p. 147)	
Tartar emetic (antimony and potassium tartrate U. S. P.)	
(White, J. C.,[3] p. 171)	
Tartaric acid [221]	Reaction on the hands and forearms of painters using the acid
Tasmanian blue gum [4]	Used in beams, sleeping cars, piers, bridges and fences
Teak [8]	Used in ship building, railroad cars, furniture and parquetry
Teakwood	The dust is irritating
	Used in ship building, railroad cars and furniture
Tetranitromethane	
(White, R. P.,[2] p. 176)	
Tetryl (tetranitromethylaniline)	
Tetterberry	Redness and vesicles
(White, J. C.,[3] p. 92)	The fresh plant is irritating

216. Cronin, H. J.: Lead Stearate Poisoning in Rubber Industry, Boston M. & S. J. **192**:900 (May 7) 1925.

217. Porosz, M.: Eczema from Dye in Stockings, Dermat. Wchnschr. **78**: 510 (May 3) 1924.

218. Schwartz, Louis: Actual Causes of Dermatitis Attributed to Socks, Pub. Health Rep. **49**:1176 (Oct. 5) 1934.

219. Danbolt, N.: Eczema Due to Suppositories in Persons Hypersensitive to Quinine, Norsk mag. f. lægevidensk. **92**:623 (June) 1931.

220. Sequeira,[210] p. 77.

221. Combalat, Paul: Étude des dermatoses professionelles, Paris, G. Steinheil, 1894, p. 41.

Cutaneous Irritants	Comment
Tetterwort ..... (White, J. C.,[3] p. 115)	Redness and vesicles The fresh juice is irritating
Thorium	
Tin-foil [222]	Rolling and beating the tin-foil cause a great amount of dust; there is no reason why the dust should irritate
Tincture of benzoin (compound tincture of benzoin U. S. P.)[223]	
Tincture of capsicum..... (White, J. C.,[3] p. 131)	Long exposure is necessary to cause irritation
Tincture of iodine..... (White, J. C.,[3] p. 160)	
"Tint as you rinse" [224].....	Erythematous patches on the buttocks and thighs from wearing of "panties," "scanties" or "stepins"
T. N. T. (trinitrotoluene)..... (White, R. P.,[2] p. 173)	Pure T. N. T. does not cause a dermatitis
Tobacco [225]	Irritation is fairly common in the process of stripping tobacco
Tobacco industry ..... (White, R. P.,[2] p. 273)	Twist is lubricated with olive oil, which is irritating
Toilet seat [226]	Reaction on the buttocks and thighs, probably produced by a red stain
Tomato plant [227] ..... (Lycopersicum)	Reaction on the hands and forearms Dermatitis is uncommon Wet vines of the plant are more irritating than dry vines
Tomatoes [228]	Reaction on the hands caused by the peeling of tomatoes in a canning factory
Tonqua bean [4]	Used as a veneer in sleeping cars and on canes, umbrella handles and fishing rods
Tooth-leaved maiden [4]	Source of dye
Traveler's joy ..... (White, R. P.,[2] p. 347)	
Tree of heaven..... (White, J. C.,[3] p. 125)	Reaction on the face Irritation during the flowering season
Trinitro-asinol ..... (White, R. P.,[2] p. 217)	
Trinitrophenol (picric acid) and butesin picrate ointment [229]	Erythematous weeping vesicular reaction affecting the anal region Used in preparation of the abdomen for surgical intervention; applied to hemorrhoids
Tulips [159]	Florist had a reaction
Turkish boxweed [4]	Used in engraving, pipes, flutes, knife handles and violin parts
Turpentine ..... (White, R. P.,[2] p. 281)	Decorators thin colors with turpentine in porcelain factories and pottery factories
Tsuga urushi [4]	
Typewriter ribbons	
Uatara [4]	
Upas tree ..... (White, J. C.,[3] p. 74)	Erysipelatous swelling due to contact with tree Cultivated in botanic gardens
Upholstery [230]	Urticaria-like papular reaction on the forearms due to contact with a new upholstered easy chair The dye used in the upholstery was Bindscheler's green, one of the paraphenylendiamine dyes

222. Fisch, F.: Zinc, Tin, Nickel, in Ullmann, K.; Oppenheim, M., and Rille, J. H.: Die Schädigungen der Haut durch Beruf und gewerbliche Arbeit, Leipzig, Leopold Voss, 1925, vol. 2, pp. 140-142.

223. James, B. M.: Dermatitis Produced by Compound Tincture of Benzoin, J. M. Soc. New Jersey **27**:596 (July) 1930.

224. Chipman, Ernest D.: Dermatitis from Dyed Garments, Arch. Dermat. & Syph. **33**:537 (March) 1936.

225. Overton, S. G., in Annual Report of H. M. Chief Inspector of Factories, 1929, p. 86.

226. Cummer C. L.: "Toilet Seat Dermatitis" Produced by a Red Stain: Possibility of Sudan Stain as Causative Factor, Arch. Dermat. & Syph. **27**: 976 (June) 1933.

227. Lain, E. S.: Dermatitis Lycopersicum Esculentum (Tomato Plant), J. A. M. A. **71**:1114 (Oct. 5) 1918.

228. Foà, G.: Professional Eczema, Policlinico (sez. prat.) **34**:675 (May 9) 1927.

229. Jackson, N. R.: Dermatitis from Picric Acid Solution and Butesin Picrate Ointment, Arch. Dermat. & Syph. **21**:40 (Jan.) 1930.

230. Dermatitis from Dyes, Correspondence, J. A. M. A. **93**:402 (Aug. 3) 1929.

Cutaneous Irritants	Comment
Urotropine (hexamethylenetetramine; methenamine U. S. P.) (White, R. P.,[2] p. 252)	Used in the rubber tire industry as an accelerator In hot weather the urotropine, mixing with sweat which is slightly acid, is changed into formaldehyde; a mild alkali is a convenient antidote
Ursol D (paraphenylendiamine)	A dye employed by furriers; black and brown fur are more often irritating than others; fur is more irritating when wet
Vaginal suppositories [231]	Reaction on the genitals of men and women The irritant is quinine
Vanilla (Vanilla plantifolia) (White, R. P.,[2] p. 355)	Erythema and papules on the wrists and forearms Used as a perfume, as a flavoring ingredient and for confectionery purposes
Varnish (fresh)[232]	Affects cleaners, packers and sorters of the pod Used on heddle frames in cotton mills The active irritant is ceresin
Vaseline (petrolatum)	The literature fails to show reports of dermatitis from pure vaseline; this is not surprising, for vaseline is one of the most stable bodies known to chemists and does not contain phenol, cresol or any saponifiable matter; I believe it possible that pigmentation may follow the prolonged and continued use of vaseline; impure vaseline can cause a dermatitis and melanoderma. A few persons working with impure vaseline have been troubled with acne and folliculitis; in looking over various cosmetic formulas, I find that vaseline is used in only a few; it deserves more consideration because of the advantage of its never becoming rancid and being nonirritating
Vinhatico amorella [4]	
Virgin's bower (White, J. C.,[3] p. 118)	Vesicles on the skin of workers
Viscose (White, R. P.,[2] p. 264)	Reaction on the fingers of persons working in the bleaching section of a viscose factory
Vleminckx' solution (solution of sulfurated lime U. S. P.) (White, J. C.,[3] p. 160)	Redness, papules, vesicles
Wall paper cleaner [4]	Used in cabinet making, turnery and gun-stocks
Walnut [3]	
Washing	Redness, vesicles in washer women The irritant is lye
Water glass (sodium silicate, U. S. P.)	Used in laundry soap, in woods to make them noncombustible, in silk to make it heavy, as preservative for eggs and in surgical work to make immovable bandages
Water pepper (White, J. C.,[3] p. 117)	Reaction on the hands and face of collectors of plants
Water plantain (White, J. C.,[3] p. 31)	
Waterproof material [233]	Dermatitis without direct contact occurs on exposed parts Common agents used to plasticize rubber in making waterproof garments are benzene, gasoline, petroleum benzine and coal tar naphtha Workmen are usually affected
Water softeners [234]	Softeners contain potassium sodium and aluminum silicate Trade substances are zealite, permutite, green sand and sodium carbonate Irritating soaps and toilet articles are more to blame than water and its contents
Wave lotion [235]	Used to maintain the waves of the hair
West Indian satinwood [4]	Used in furniture, cabinet work, inlay and turnery, backs of brushes and mirrors
White alder [4]	
White pine [4]	Used in desks, flooring and matches

231. Danbolt, N.: Eczema Due to Suppositories in Persons Hypersensitive to Quinine, Norsk mag. f. lægevidensk. **92**:623 (June) 1931.

232. Schwartz, Louis, and Pool, Charles L.: Outbreak of Dermatitis in Cotton Mills Due to Varnish, J. Indust. Hyg. **15**:214 (July) 1933.

233. Dermatitis in Manufacturing Water-Proof Material, Queries and Minor Notes, J. A. M. A. **93**:1010 (Sept. 28) 1929.

234. Water Softeners and Dermatitis, Queries and Minor Notes, J. A. M. A. **103**:281 (July 28) 1934.

235. Rattner, H.: Dermatitis of the Eyelids, J. A. M. A. **103**:180 (July 21) 1934.

Cutaneous Irritants	Comment
White weed ..... (White, J. C.,[8] p. 88)	Papules and vesicles on the fingers from picking flowers
Wigandia caracasano [236]	
Witch hazel (hamamelis leaf N. F.)	
Women's hats [237]	Persistent dermatitis on the head where it is in contact with the hat, i. e., the lower part of the occiput, the tips of the ears, the temples and to a lesser degree the neck and forehead
Wood preserving materials [238].....	Reaction on exposed parts Active irritants: coal tar distillates, water gas tar and zinc chloride Irritation occurs more often during hot weather
Wool [239]	
Wool fat [240]	
Wool, washing of.....	Reaction on the hands and forearms Irritants: aniline, arsenic
Wrist watch [241]	Reaction at the point of contact with a watch The active irritant is nickel
Wrist watch strap [242].....	Unilateral reaction The irritant is amino-azotoluene, a dye
X-rays and radium [243].....	
Yellow jessamine ..... (White, J. C.,[8] p. 110)	Reaction in collectors of the roots
Yellow wood [4]	
Yew tree [4]	Used in archery bows, turnery, tops, canes and chairs
Zinc oxide plaster [244].....	Dermatitis conforms to the outline of the plaster on the part to which the plaster is applied

II Occupations which Are Frequently a Cause of Dermatitis [245]

Occupation	Irritant Handled
Acetaldehyde makers.....	Mercury
Acetanilid workers.....	Aniline
Acetic acid makers.....	Hydrochloric acid
Acetic acid makers (synthetic).....	Mercury
Acetone workers.....	Acetone
Acetone makers (synthetic).....	Mercury and its compounds
Acetylene workers.....	Acetone Ammonia Carbon disulfide Chloride of lime (calcium chloride U.S.P.) Chromium compounds

236. Anderson, N. P., and Ayres, S.: Dermatitis Venenata Due to Wigandia Caracasana, Hitherto Unrecognized Cause: Report of a Case, California & West. Med. **34**:278 (April) 1931.

237. Frei, W.: Eczema of the Head Caused by Women's Hats, Deutsche med. Wchnschr. **57**:55 (Jan. 9) 1931.

238. Dermatitis from Wood Preserving Materials, Queries and Minor Notes, J. A. M. A. **97**:799 (Sept. 12) 1931.

239. Lord, L. W.: Cutaneous Sensitization to Wool, Arch. Dermat. & Syph. **26**:707 (Oct.) 1932.

240. Sulzberger, M. B., and Morse, J. L.: Hypersensitiveness to Wool Fat, J. A. M. A. **96**:2099 (June 20) 1931.

241. Dermatitis from Wrist Watch, Foreign Letter, J. A. M. A. **99**:1006 (Sept. 17) 1932.

242. Schwartz, L.: Dermatitis from Wrist Watch Straps, Pub. Health Rep. **51**:423 (April 10) 1936.

243. MacKee, George M.: X-Ray and Radium in the Treatment of Diseases of the Skin, Philadelphia, Lea & Febiger, 1927.

244. Dermatitis from Zinc Oxide Plaster, Queries and Minor Notes, J. A. M. A. **94**:1430 (May 3) 1930.

245. In making out this table much information was obtained from Rosenau's work (Rosenau, Milton J., and others: Preventive Medicine and Hygiene, ed. 6, New York, D. Appleton & Company, 1927).

Occupation	Irritant Handled
Acid dippers	Cyanogen compounds
	Hydrochloric acid
	Nitrous gases
	Nitrosulfuric acid
Acid finishers (glass)	Hydrochloric acid
	Sulfuric acid
Acid mixers	Hydrochloric acid
	Nitrous gases and nitric acid
	Sulfuric acid
Acid recoverers	Hydrochloric acid
	Nitrous gases and nitric acid
	Sulfuric acid
Acid transporters	Hydrochloric acid
	Nitrous gases and nitric acid
	Sulfuric acid
Acridine workers	Acridine
Acrolein workers	Acrolein
Agricultural implement makers	Bassia wood
Airplane wing makers	Tetrachlorethane
Airplane dope makers	Acetone
	Amyl acetate
	Benzene
	Carbon tetrachloride
	Tetrachlorethane
Alcohol distillery workers	Amyl acetate
	Amyl alcohol
Alcohol fermenters	Formic acid
Alcohol workers (denatured)	Benzene
Alcohol makers (synthetic)	Mercury
Aldehyde pumpmen	Methanol (methyl alcohol)
Alkali salt makers	Chlorine
	Hydrochloric acid
	Sulfuric acid
Alum workers	Hydrofluoric acid
Aluminum extractors	Mercury
Amalgam makers	Ammonia
Ammonia workers	Cyanogen compounds
Ammonium salts makers	Sulfuric acid
	Hydrochloric acid
Amyl acetate makers	Amyl alcohol
Amyl acetate workers	Amyl acetate
Aniline compound workers	Chromium compounds
Aniline dye makers	Methanol (methyl alcohol)
Aniline makers	Benzene
	Hydrochloric acid
	Nitro-aniline
	Nitrous gases and nitric acid
Aniline workers	Aniline
Antifreeze makers	Methanol (methyl alcohol)
Antimony extractors (refiners)	Antimony
Antimony fluoride extractors	Hydrofluoric acid
Antipyrine makers	Phenylhydrazine
Arsenic roasters	Arsenic
Artificial amber makers	Formaldehyde
Artificial flower makers	Arsenic
	Chromium compounds
	Mercury
	Methanol (methyl alcohol)
Artificial ice makers	Ammonia
Artificial leather makers	Acetone
	Aniline
	Arsenic and its compounds
	Benzene
	Nitrous gases and nitric acid
	Sulfuric acid
Artificial leather workers	Amyl acetate
	Butyl alcohol
Artificial pearl makers	Amyl acetate
	Nitrous gases and nitric acid
	Tetrachlorethane
Artificial resin makers	Cresol
Artificial silk makers	Tetrachlorethane
	Ammonia
	Amyl acetate
	Carbon disulfide
	Cyanogen compounds
	Formaldehyde
	Hydrochloric acid
	Methanol (methyl alcohol)
	Sulfuric acid
Artificial silk workers	Butyl alcohol
	Sodium hydroxide

Occupation	Irritant Handled
Artificial stone makers	Tar
Art glass workers	Hydrofluoric acid
	Methanol (methyl alcohol)
	Turpentine
	Amyl acetate
	Benzine
	Methanol (methyl alcohol)
Art printing workers	Cyanogen compounds
Asphalt testers	Carbon disulfide
Asphalt workers	Tar
Automobile painters	Methanol (methyl alcohol)
Bakelite makers	Formaldehyde
	Phenol
Barometer makers	Mercury
Battery (dry) makers	Amyl acetate
	Benzene
	Chromium compounds
	Hydrochloric acid
	Mercury
	Tar
Battery makers (storage)	Antimony
Beam makers	Burma padouk
	Tasmanian blue gum
Beater men (paper and pulp)	Chlorine
Benzine purifiers	Sulfuric acid
Benzene still men	Benzene
Betanaphthol still operators	Sulfuric acid
Billiard table makers	Brazilian rosewood
	Purple wood
Billiard cue makers	Purple wood
	Santo wood
Blacksmiths	Cyanogen compounds
Blast-furnace workers	Cyanogen compounds
Bleachers	Chloride of lime (calcium chloride U.S.P.)
	Chlorine
	Chromium compounds
	Hydrochloric acid
	Hydrofluoric acid
	Nitrous gases and nitric acid
	Potassium hydroxide
	Sodium hydroxide
Bleaching powder makers	Chloride of lime (calcium chloride U.S.P.)
Blenders (motor fuel)	Benzene
Blind makers	Lawson's cypress
Blowers (felt hats)	Mercury
Blue-print makers	Chromium
Boat builders	Peroba
	Poplar
	Silver sprucewood
Bone-black makers	Ammonia
	Phosphorus
Bone distillers	Cyanogen compounds
Bone renderers	Acrolein
Bookbinders	Amyl acetate
	Methanol (methyl alcohol)
	Arsenic
Bottle cleaners	Acetic acid
Bowling ball makers	Ironwood
	Coco-bolo
	Lignum vitae
Box makers	Canadian spruce
Brake lining makers	Benzene
Brass founders	Antimony
	Arsenic
	Carbon dioxide
	Phosphorus
Brewers	Hydrofluoric acid
	Phenol
Bridge makers	Karri
	Tasmanian blue gum
Briquet makers	Arsenic
	Tar
Bromine makers	Chlorine
Bromine salts makers	Bromine
Bronze object cleaners	Acetic acid

Occupation	Irritant Handled
Bronzers	Ammonia Amyl acetate Arsenic Benzine Benzene Cyanogen compounds Hydrochloric acid Mercury Methanol (methyl alcohol)
Broom makers	Chlorine Formaldehyde
Browners (gun barrels)	Cyanogen compounds Mercury Petroleum
Brush back makers	Ironwood Coco-bolo East Indian satinwood Granadilla West Indian satinwood
Brush makers	Formaldehyde Methanol (methyl alcohol) Tar
Brushers (felt hats)	Mercury
Buffers (rubber)	Amyl acetate Benzine
Burnishers (iron and steel)	Antimony Sulfuric acid
Burnishers (rifle barrels)	Antimony
Butyl alcohol makers	Butyl alcohol
Cabinet workers	African mahogany Antilles satinwood Atlas satinwood Australian blackwood Brazilian rosewood Brazilian walnut Bigalow spearwood Jarrah wood Kingwood Laburnum Lemon wood Mahogany Manchineel Purple wood Queensland maple Red bean Red satinwood Sand-box tree Sea grape Spotted gum Surinam greenheart Walnut West Indian satinwood
Cabinet (fine) workers	African boxwood Yellow gray box
Cable splicers	Turpentine
Calcium carbide makers	Ammonia
Calico printers	Amyl acetate Aniline Antimony Arsenic Cadmium Chlorine Chromium compounds Cyanogen compounds Formaldehyde Hydrochloric acid Mercury Methanol (methyl alcohol) Nitrous gases and nitric acid Phenol Sulfuric acid Turpentine
Camphor makers	Amyl acetate Aniline Hydrochloric acid Turpentine
Can makers (sanitary)	Benzene
Candle makers	Acrolein

Occupation	Irritant Handled
Candle makers (colored)	Arsenic Chromium compounds
Canes	Snakewood Tonca bean Yew tree
Cap loaders	Mercury
Carbolic acid (phenol) makers	Benzene Phenol Sulfuric acid
Carbon printers (photography)	Chromium compounds
Carbonilide makers	Carbon disulfide
Carbonizers (shoddy)	Hydrochloric acid Sulfuric acid
Carbon tetrachloride workers	Carbon tetrachloride
Card case makers	Common alder
Carpentry	West Indian locust Fustic Jacareuba
Carpet makers	Arsenic
Carroters (felt hats)	Arsenic Mercury Nitrous gases and nitric acid
Cartridge dippers	Hydrochloric acid Nitrous gases and nitric acid Sulfuric acid
Cartridge makers	Mercury
Carvers	Block bean Macassas wood South African boxwood
Case hardeners	Cyanogen compounds
Casket makers	Lawson's cypress
Cast scrubbers (electroplaters)	Benzine Benzene
Cellulose acetate makers	Acetone
Cellulose acetate workers	Tetrachlorethane
Cellulose formate makers	Formic acid
Cellulose workers	Carbon disulfide
Cement makers	Hydrochloric acid
Cementers (rubber)	Turpentine
Cementers (rubber shoes)	Benzine Benzene Carbon disulfide Carbon tetrachloride Methanol (methyl alcohol)
Cement mixers (rubber)	Benzine Benzene Carbon disulfide Carbon tetrachloride
Chair makers	Yew tree
Chamber men (sulfuric acid)	Sulfuric acid
Chargers (zinc smelting)	Arsenic
Chauffeurs	Benzine
Chimney sweepers	Arsenic Tar
Chloride of lime makers	Chloride of lime Chlorine
Chlorine compound makers	Hydrochloric acid
Chlorine makers	Hydrochloric acid
Chlorine makers (electrolytic makers)	Mercury
Chlorine workers	Chlorine
Chloroform makers	Acetone Chloride of lime
Chrome workers	Chromium compounds
Chromium platers	Chromium compounds
Cigaret case makers	Common alder
Clarinet makers	Granadilla
Coal tar distillery workers	Cyanogen compound
Coal tar workers	Aniline Benzene Cresol Phenol Tar
Coffin makers	Lawson's cypress
Coke oven workers	Ammonia Benzene Tar
Collodion workers	Nitrous gases and nitric acid

Occupation	Irritant Handled
Color makers	Ammonia
	Antimony
	Arsenic
	Benzene
	Bromine
	Cadmium
	Chlorine
	Chromium
	Mercury
	Sulfuric acid
	Tetrachlorethane
	Thallium
Colored paper workers	Arsenic
Compositors	Aniline
	Antimony
	Benzine
Compounders (rubber)	Aniline
	Antimony
	Arsenic
	Benzine
	Chromium compounds
Coners (felt hats)	Mercury
Construction (general)	Greenheart
	Poplar
	West Indian locust
Construction (heavy)	Brauna
	Massaranduba
	Partridge wood
Construction workers	Aroeira
	Bassia wood
	Borneo cedar
	Canadian spruce
	Chestnut
	Brazilian walnut
	Jacareuba
	Jarrah wood
	Peroba perdu
Copper founders	Arsenic
Copper refiners	Antimony
Copper smelters	Arsenic
Cosmetic workers	Mercury
Crate makers	Canadian spruce
Crayon (colored) makers	Chromium compounds
Creosoting plant workers	Tar
Cresol soap makers	Cresol
Cresylic acid makers	Cresol
Curriers (tannery)	Arsenic
	Benzine
Cut glass workers	Arsenic
Cutlery handle makers	Santo wood
Cutlery makers	Amyl acetate
Cyanide makers	Ammonia
Cyanide workers	Cyanogen compounds
Cyanogen makers	Mercury
Deck makers	White pine
Decorative panel workers	African padouk
	Vermilion mahogany
Decorative workers	Antilles satinwood
	Burma padouk
Decorators (pottery)	Arsenic
	Benzine
	Benzene
	Turpentine
Degreasers (fertilizers; leather)	Benzine
	Benzene
Degreasers (textiles)	Carbon tetrachloride
Denatured alcohol workers	Pyridine
Dentists	Mercury
Depilatory makers	Thallium
Detinning workers	Chlorine
Detonator cleaners	Mercury
Detonator fillers	Mercury
Detonators packers	Mercury
Devil operators (felt hats)	Mercury

Occupation	Irritant Handled
Dimethyl sulfate makers	Dimethyl sulfate Methanol Nitrous gases and nitric acid Sulfuric acid
Dippers (guncotton)	Nitrous gases and nitric acid
Dippers (rubber)	Benzine Benzene
Disinfectant makers	Chloride of lime Chlorine Cresol Mercury Thallium
Disinfectant workers	Bromine Cyanogen compounds Formaldehyde Phenol
Door makers	Lawson's cypress
Door and window sash makers	Silver sprucewood
Dope workers	Tetrachlorethane
Drain pipe makers	Common alder
Driers (felt hats)	Methanol (methyl alcohol)
Driers (rubber)	Benzine Benzene Carbon disfulfide
Drinking cup makers	Lignum nephriticum
Drumstick makers	Snakewood
Dry Cleaners	Benzine Benzene Carbon disulfide Carbon tetrachloride Methanol (methyl alcohol) Oxalic acid Turpentine
Dye makers	Acetone Acridine Ammonia Aniline Antimony Arsenic Benzene Bromine Chloride of lime (calcium chloride U.S.P.) Chlorine Chromium compounds Cresol Cyanogen compounds Dimethyl sulfate Formaldehyde Formic acid Hydrochloric acid Mercury and its compounds Methanol (methyl alcohol) Methyl chloride Nitrobenzene Nitrous gases and nitric acid Oxalic acid Phenol Phenylhydrazine Phosgene (carbonyl chloride) Picric acid (trinitrophenol U.S.P.) Sulfuric acid Turpentine
Dye (source of)	Carosco (Puerto Rico) Guao Tooth-leaved maiden
Dye wood	Brazil wood
Dyers	Acetone Amyl acetate Aniline Benzine Chromium compounds Hydrochloric acid Hydrofluoric acid Phenol Picric acid (trinitrophenol U.S.P.)
Electric induction (furnace workers)	Mercury
Electrode makers	Tar

Occupation	Irritant Handled
Electroplaters	Antimony
	Arsenic
	Benzine
	Benzene
	Carbon disulfide
	Carbon tetrachloride
	Chromium compounds
	Cyanogen compounds
	Formic acid
	Hydrochloric acid
	Mercury
	Nitrous gases and nitric acid
	Sulfuric acid
Electrotypers	Aniline
Embalmers	Formaldehyde
	Mercury
Embossers	Mercury
Enamelers	Amyl acetate
	Arsenic
	Benzine
	Benzene
	Carbon disulfide
	Chromium compounds
	Tetrachlorethane
	Turpentine
Enamel workers	Amyl acetate
	Aniline
	Arsenic
	Benzine
	Benzene
	Carbon disulfide
	Chromium compounds
	Hydrochloric acid
	Nitrous gases and nitric acid
	Tetrachlorethane
	Turpentine
Engravers	Benzene
	Hydrochloric acid
	Oxalic acid
	Sulfuric acid
	South African boxwood
	Turkish boxwood
Etchers	Hydrochloric acid
	Hydrofluoric acid
	Nitrous gases and nitric acid
	Phenol
	Sulfuric acid
Ether makers	Sulfuric acid
Ethylene dibromide makers	Bromine
Explosive workers	Acetone
	Ammonia
	Amyl acetate
	Amyl alcohol
	Aniline
	Benzene
	Carbon disulfide
	Cresol
	Formaldehyde
	Mercury
	Methanol (methyl alcohol)
	Nitro-aniline
	Nitrobenzene
	Nitroglycerin
	Nitrous gases and nitric acid
	Phenol
	Picric acid (trinitrophenol U.S.P.)
	Sulfuric acid
Explosives (ammonia and pyroxylin) workers	Chromium compounds
Extractors (gold and silver)	Chlorine
	Cyanogen compounds
	Mercury
Extractors (oil and fats)	Benzene
Farmers	Arsenic
Fat purifiers	Sulfuric acid
Fat renderers	Acrolein
Feather curers	Arsenic
Feather workers	Aniline
	Arsenic
	Benzine
	Benzene
	Methanol (methyl alcohol)
	Petroleum
	Turpentine
Felly makers (for cart wheels)	Citrus wood

Occupation	Irritant Handled
Felt hat makers	Arsenic
	Mercury
	Methanol (methyl alcohol)
	Sulfuric acid
Fence post makers	Fustic
	Surinam snakewood
Ferrosilicon	Arsenic
Fertilizer makers	Ammonia
	Cyanogen compounds
	Hydrochloric acid
	Hydrofluoric acid
	Manganese
	Nitrous gases and nitric acid
	Phosphorus
	Sulfuric acid
Fertilizer workers	Carbon dioxide
Filament makers (incandescent lamps)	Methane
	Thallium
Filers	Antimony
Fire extinguisher makers	Carbon tetrachloride
Fireman (city)	Carbon tetrachloride
Fireworks makers	Antimony
	Arsenic
	Mercury
	Phosphorus
	Picric acid (trinitrophenol U.S.P.)
Fishing rod makers	Surinam greenheart
	Tonca bean
Fitters (shoes)	Methanol (methyl alcohol)
Floor makers	Brauna
	Karri
	Lemon wood
	Peroba perdu
	White pine
Floor polish makers	Nitro-aniline
Flue cleaners	Tar
Flute makers	Granadilla
	Turkish boxwood
Formic acid makers	Formic acid
Fountain makers	Lignum nephriticum
Frosters (glass and pottery)	Chromium compounds
Fruit essence makers	Amyl acetate
	Amyl alcohol
Fuel makers	Fustic
	Suriname snakewood
Fulminate mixers	Cyanogen compounds
Fumigators	Cresol
	Cyanogen compounds
Fur handlers	Arsenic
	Mercury
Fur preparers	Arsenic
	Mercury
	Nitrous gases and nitric acid
Furniture (fine)	Borneo rosewood
	Rengas
	Singapore mahogany
Furniture makers	African mahogany
	African padouk
	Audiroba
	Australian silky oak
	Black bean
	Borneo cedar
	Brauna
	Brazilian satinwood
	Brazilian walnut
	East Indian satinwood
	Indian jungle wood
	Indian rosewood
	Jacareuba
	Kingwood
	Lemon wood
	Mahogany
	Massaranduba
	Muirapanga
	Peroba perdu
	Poison wood
	Red bean
	Red satinwood
	Sabicu
	Sand-box tree
	Satin nut wood
	Sea grape
	Teak
	West Indian satinwood

Occupation	Irritant Handled
Furniture polishers	Amyl acetate
	Benzine
	Chromium compounds
	Methanol (methyl alcohol)
	Petroleum
	Turpentine
Fusel oil (amyl alcohol) workers	Amyl alcohol
Galvanizers	Ammonia
	Arsenic
	Hydrochloric acid
	Nitrous gases and nitric acid
	Sulfuric acid
Garage workers	Benzine
Gardeners	Arsenic
Gas purifiers	Ammonia
	Cyanogen compounds
	Phenol
Gas (illuminating) workers	Ammonia
	Benzene
	Cyanogen compounds
	Phenol
	Tar
Gasoline engine workers	Benzine
Germicide makers	Aniline
	Formaldehyde
	Picric acid (trinitrophenol U.S.P.)
Gilders	Amyl acetate
	Benzine
	Benzene
	Cyanogen compounds
	Mercury
	Methanol (methyl alcohol)
	Nitrous gases and nitric acid
	Pyridine
Glass colorers	Chromium compounds
Glass etchers	Formaldehyde
Glass finishers	Hydrochloric acid
	Hydrofluoric acid
	Sulfuric acid
Glass mixers	Antimony
	Arsenic
	Hydrochloric acid
Glass workers	Thallium
Glaze dippers (pottery)	Antimony
	Arsenic
Glaze mixers (pottery)	Antimony
	Arsenic
	Hydrochloric acid
Glaze workers (pottery)	Chromium compounds
Glazers (pottery)	Hydrochloric acid
Glue makers	Acrolein
	Ammonia
	Carbon dioxide
	Hydrochloric acid
	Sulfuric acid
Glue workers	Benzine
	Benzene
	Carbon disulfide
Glycerin refiners	Oxalic acid
Gold extractors	Bromine
Gold refiners	Arsenic
	Cyanogen compounds
	Hydrofluoric acid
	Mercury
Grinders (metals)	Aniline
Grinders (rubber)	Aniline
Guncotton dippers	Sulfuric acid
Guncotton workers	Nitrous gases and nitric acid
Gunstock workers	Walnut
Gunstock hard woodwork	California cedar
Hardener (felt hats)	Mercury
	Methanol (methyl alcohol)
Hat makers	Acetic acid
House construction workers	Andiroba
	Peroba
Hub makers (for cart wheels)	Citrus wood
Hydrochloric acid makers	Hydrochloric acid
	Sulfuric acid
Hydrofluoric acid makers	Hydrofluoric acid

Occupation	Irritant Handled
Hydrocyanic acid makers	Cyanogen
	Sulfuric acid
Incandescent lamp makers	Mercury
	Methanol (methyl alcohol)
Ink makers	Bromine
	Chlorine
	Chromium compounds
	Formaldehyde
	Hydrochloric acid
	Methanol (methyl alcohol)
	Nitro-aniline
	Oxalic acid
Inlayers	African ebony
	Coco-bolo
	Laburnum
	Macassar wood
	Molucca ebony
	Olive wood
	Poison wood
	Purple wood
	South African boxwood
	West Indian satinwood
Insecticide makers	Arsenic
	Carbon disulfide
	Formaldehyde
	Phosphorus
Insulators	Tar
Interior trimmers	African mahogany
	Brazilian walnut
	Mahogany
	Sabicu
	Sand-box tree
Interior work	Black bean
	Poplar
Iodine makers	Chlorine
Japanese lacquer makers	Arsenic
	Benzine
	Methanol (methyl alcohol)
	Turpentine
Japanners	Arsenic
	Benzine
	Methanol (methyl alcohol)
Jewelers	Amyl acetate
	Cyanogen compounds
	Hydrochloric acid
	Mercury
	Nitrous gases and nitric acid
	Sulfuric acid
Joiners	Australian blackwood
Knife handle makers	Coco-bolo
	Turkish boxwood
Laboratory workers	Mercury
Lacquerers	Acetone
	Amyl acetate
	Amyl alcohol
	Arsenic
	Benzine
	Benzene
	Carbon tetrachloride
	Formic acid
	Methanol (methyl alcohol)
	Pyridine
	Tetrachlorethane
	Turpentine
Lacquer makers	Acetone
	Ammonia
	Amyl acetate
	Amyl alcohol
	Arsenic
	Benzine
	Benzene
	Carbon tetrachloride
	Formic acid
	Lacquer tree
	Methanol (methyl alcohol)
	Pyridine
	Tetrachlorethane
	Turpentine
Lampblack makers	Petroleum
	Phenol
Lard makers	Acrolein

Occupation	Irritant Handled
Lasters (shoes)	Methanol (methyl alcohol)
Laundry workers	Chloride of lime (calcium chloride U.S.P.) Chlorine
Lead smelters	Aniline Arsenic
Leather workers	Amyl acetate Hydrochloric acid
Linoleum colorers	Arsenic
Linoleum makers	Acrolein Amyl acetate Benzine Methanol (methyl alcohol) Sulfuric acid Turpentine
Linoleum workers	Benzol Chromium compounds
Linotypers	Antimony
Linseed oil boilers	Acrolein
Lithographers	Aniline Arsenic Benzine Benzene Chromium compounds Hydrochloric acid Mercury Nitrous gases and nitric acid Oxalic acid Sulfuric acid Tetrachlorethane Turpentine
Manometer makers	Mercury
Match factory workers	Carbon disulfide Chromium compound Phosphorus Potassium hydroxide White pine Sodium hydroxide Sulfuric acid
Mercury alloy makers	Mercury
Mercury boiler workers	Mercury
Mercury bronzers	Mercury
Mercury miners	Mercury
Mercury pump workers	Mercury
Mercury salt workers	Mercury
Mercury smelters	Mercury
Mercury still cleaners	Mercury
Mercury switch makers	Mercury
Mercury vapor lamp makers	Mercury
Metal cleaners	Hydrochloric acid
Metal refiners	Hydrochloric acid
Metal polish makers	Benzine Carbon tetrachloride Oxalic acid
Methyl alcohol makers	Acetone Methanol (methyl alcohol)
Methyl compound makers	Methanol (methyl alcohol)
Millinery workers	Aniline Benzine Benzene Methanol (methyl alcohol) Petroleum Turpentine
Mirror silverers	Ammonia Cyanogen compounds Formaldehyde Formic acid Mercury
Mixers (felt hats)	Mercury
Mixers (rubber)	Aniline Arsenic Benzine Benzene Chromium compounds
Monotypers	Antimony

Occupation	Irritant Handled
Mordant makers	Amyl alcohol Antimony Arsenic Benzine Benzene Chloride of lime (calcium chloride U.S.P.) Chromium compounds Cyanogen compounds Formic acid Nitrous gases and nitric acid
Motion picture film makers	Tetrachlorethane
Motion picture film workers	Butyl alcohol
Motor car body workers	Australian blackwood
Nitro-aniline workers	Aniline
Nitrate makers	Nitrous gases and nitric acid Sulfuric acid
Nitric acid makers	Ammonia Nitrous gases and nitric acid Sulfuric acid
Nitric acid workers	Nitrous gases and nitric acid
Nitrobenzine makers	Benzene Sulfuric acid
Nitrobenzene workers	Nitro-aniline
Nitrocellulose makers	Nitrous gases and nitric acid Sulfuric acid
Nitrocellulose workers	Acetone Amyl alcohol Benzene
Nitroglycerin makers	Nitrous gases and nitric acid Sulfuric acid
Nitroglycerin workers	Nitroglycerin
Nitrous oxide workers	Nitrous gases and nitric acid
Oars, makers of	Silver sprucewood
Oil extractors	Acetone Carbon disulfide Tetrachlorethane
Oil flotation plant workers	Petroleum
Oil purifiers	Sulfuric acid
Oil refiners	Sodium hydroxide
Oil well workers	Petroleum
Oilcloth makers	Benzene
Ornamental workers	Borneo redwood Rengas Singapore mahogany
Ox yoke makers	Peroba
Oxalic acid makers	Cyanogen compounds
Oxalic acid workers	Oxalic acid
Paint makers	Acetone Amyl acetate Aniline Arsenic Benzine Benzene Carbon disulfide Chromium compounds Hydrochloric acid Mercury Methanol (methyl alcohol) Phenol Tar Turpentine
Paint removers	Acetone Amyl acetate Benzene Phenol Tetrachlorethane
Paint remover makers	Benzene Phenol Tetrachlorethane
Painters	Acetone Amyl acetate Aniline Arsenic Benzine Benzene Carbon disulfide Chromium compounds Mercury Methanol (methyl alcohol) tar Turpentine

Occupation	Irritant Handled
Panel makers	East Indian satinwood Kingswood Macassar wood
Paneling	Borneo cedar Red bean
Paper glazers	Arsenic
Paper hangers	Arsenic Chromium compounds
Paper makers	Canadian spruce Chlorine Formaldehyde Sulfuric acid Sodium hydroxide
Paper-pulp workers	Spruce
Paraffin makers	Benzene
Paraffin workers	Acetone Carbon disulfide Carbon tetrachloride Petroleum Tar
Paris green workers	Arsenic
Parquet floor workers	Australian silky oak Kingwood Granadilla
Patent leather makers	Amyl acetate Sulfuric acid Turpentine
Pavers	Tar
Paving block makers	Jarrah wood Satin nut wood
Pencil makers	Pyridine Mountain cedarwood
Pencil (colored) makers	Aniline Arsenic Chromium compounds
Perfume makers	Acetone Amyl acetate Aniline Butyl alcohol Carbon tetrachloride Dimethyl sulfate Methanol (methyl alcohol) Nitro-aniline Phenol Spanish jasmine Sulfuric acid
Perfume (synthetic) makers	Cresol
Petroleum refiners	Ammonia Benzine Hydrochloric acid Petroleum Sulfuric acid Tar
Phenol makers	Benzol Sulfuric acid
Phenol workers	Phenol
Phenylhydrazine workers	Phenylhydrazine
Phonograph cabinet makers	Brazilian rosewood
Phosgene makers	Chlorine
Phosphate extractors	Hydrochloric acid
Phosphate mill workers	Phosphorus
Phosphor bronze workers	Phosphorus
Phosphoric acid makers	Cyanogen compounds Nitrous gases and nitric acid Sulfuric acid
Phosphorus compound makers	Phosphorus
Phosphorus evaporating machine workers	Sulfuric acid
Phosphorus extractors	Hydrochloric acid Hydrofluoric acid Phosphorus
Photograph engravers	Benzene Chromium compounds Methanol (methyl alcohol) Nitrous gases and nitric acid
Photographers	Methanol (methyl alcohol)
Photographic film makers	Amyl acetate Bromine Butyl alcohol Silver

Occupation	Irritant Handled
Photographic workers	Acetone Aniline Benzene Chlorine Chromium compounds Cyanogen Formaldehyde Hydrochloric acid Mercury Picric acid (trinitrophenol U.S.P.) Sulfuric acid
Photogravure workers	Chromium compounds
Piano makers	Vermilion mahogany
Picklers	Cyanogen compounds
Picklers (metal)	Hydrochloric acid Nitrous gases and nitric acid Sulfuric acid
Picric acid (trinitrophenol) makers	Benzene Nitrous gases and nitric acid Phenol Sulfuric acid
Picric acid (trinitrophenol) workers	Picric acid (trinitrophenol U.S.P.)
Pipe makers	Turkish boxwood
Pitch workers	Arsenic Tar
Plank makers	Burma padouk
Platinum extractors	Bromine
Ply workers	Common alder
Polish makers	Amyl acetate Benzine Methanol (methyl alcohol) Turpentine
Polishers	Benzine Turpentine
Polishers (metal)	Cyanogen compounds Oxalic acid
Polishers (wood)	Amyl alcohol Methanol (methyl alcohol)
Porcelain makers	Mercury
Pottery workers	Arsenic Hydrochloric acid
Powder (smokeless) makers	Phenol
Preservative makers and handlers	Formaldehyde
Pressroom workers (rubber)	Aniline Arsenic Benzine Turpentine
Primers (explosives)	Mercury
Printers	Aniline Arsenic Benzine Turpentine
Pulley sheaves makers	Ironwood Lignum vitae
Pullman interior workers	Vermilion mahogany
Putty makers	Benzine Carbon disulfide
Pyridine makers	Pyridine
Pyrite burners	Arsenic
Pyroxylin plastics workers	Acetone Amyl acetate Benzine Benzene Butyl alcohol Cyanogen compounds Methanol (methyl alcohol) Nitrous gases and nitric acid Sulfuric acid
Rafters	Karri
Railroad car builders	Karri
Railroad sleeper builders	Gray gum boxwood
Railroad tie makers	Moahwood
Rayon makers	Sulfuric acid
Reclaimers (rubber)	Aniline Benzene Carbon disulfide Hydrochloric acid Phenol Sulfuric acid

Occupation	Irritant Handled
Recoverers (gold and silver)	Formaldehyde
Refiners (metals)	Arsenic
	Mercury
	Nitrous gases and nitric acid
	Sulfuric acid
Refrigerating plant workers	Ammonia
Refrigerator makers and repair men	Acrolein
	Ethyl bromide
	Ethyl chloride
Resin (synthetic) makers	Cresol
	Formaldehyde
	Phenol
Rifle makers	Queensland maple
Roofers	Tar
Roofing paper workers	Tar
Rubber (artificial) workers	Cresol
Rubber glove makers	Benzine
Rubber (red) workers	Antimony
Rubber (synthetic) makers	Amyl alcohol
Rubber substitute makers	Chlorine
Rubber tire builders	Benzine
	Benzene
Rubber workers	Acetone
	Aniline
	Arsenic
	Benzine
	Benzene
	Carbon tetrachloride
	Chromium compounds
	Formaldehyde
	Formic acid
	Methanol (methyl alcohol)
	Tetrachlorethane
	Turpentine
Salt extractors (coke oven by-products)	Ammonia
	Sulfuric acid
Sandalwood oil makers	Amyris wood
	Granadilla
Sash makers	Lawson's cypress
Scourers	Nitrous gases and nitric acid
Sculptors	Macassar wood
Sealing wax makers	Arsenic
	Turpentine
Sewer workers	Ammonia
	Carbon dioxide
Shade cloth makers	Benzine
	Benzene
Sheep dip makers	Arsenic
Shell fillers	Nitroglycerin
	Picric acid (trinitrophenol U.S.P.)
Shellac makers	Ammonia
	Amyl acetate
	Benzine
	Benzene
	Butyl alcohol
	Methanol (methyl alcohol)
	Turpentine
Shellackers	Amyl acetate
	Benzine
	Benzene
	Butyl alcohol
	Methanol (methyl alcohol)
	Turpentine
Shingle makers	Satin nut wood
Ship builders	Andiroba
	Bassia wood
	Greenheart
	Moahwood
	Teak
Shoddy makers	Chlorine
Shoddy workers	Hydrochloric acid
	Sulfuric acid
Shoe dyers	Nitro-aniline
Shoe factory operators	Methanol (methyl alcohol)
Shoe factory workers	Amyl acetate
	Benzine
	Benzene

Occupation	Irritant Handled
Shoe finishers	Ammonia Amyl acetate Amyl alcohol Benzine Benzene Methanol (methyl alcohol)
Shoemakers	Antimony Arsenic
Silicate extractors	Hydrofluoric acid
Silver-foil makers	Silver
Silver melters and refiners	Silver
Silver nitrate makers	Silver
Silver platers	Silver
Silver refiners	Cyanogen compounds
Silverers	Benzene
Silverers (mirrors)	Silver
Silversmiths	Silver
Sizers (felt hats)	Mercury
Smokeless powder makers	Acetone Amyl acetate Benzene Carbon disulfide Nitro-aniline Nitrous gases and nitric acid Picric acid (trinitrophenol U.S.P.)
Soap makers	Acrolein Benzene Formaldehyde Formic acid Hydrochloric acid Methanol (methyl alcohol) Nitro-aniline Potassium hydroxide Sodium hydroxide Sulfuric acid
Soda makers	Chlorine Nitrous gases and nitric acid
Soda (la Blanc) makers	Sulfuric acid
Soda (Solvay) makers	Ammonia
Sodium hydroxide makers	Sodium hydroxide
Solderers	Cyanogen compounds Hydrochloric acid
Sole stitchers (Blake machine)	Mercury
Soot packers	Arsenic
Sprayers (trees)	Arsenic
Stablemen	Ammonia
Starters (felt hats)	Mercury
Stearic acid makers	Acrolein
Steel (chrome) workers	Chromium compounds
Steel engravers	Mercury
Stereotypers	Antimony
Stiffeners (felt hats)	Mercury Methanol (methyl alcohol)
Still (coal tar) cleaners	Benzene Tar
Stillmen (carbolic acid)	Phenol
Stitchers (shoes)	Methanol (methyl alcohol)
Storage battery makers	Mercury Sulfuric acid
Straw bleachers	Oxalic acid
Straw hat makers	Formaldehyde
Submarine workers	Chlorine
Sugar refiners	Ammonia Carbon dioxide Hydrochloric acid Sulfuric acid
Sulfate makers	Sulfuric acid
Sulfur burners	Arsenic
Sulfur chloride makers	Chlorine Hydrochloric acid
Sulfur extractors	Carbon disulfide

Occupation	Irritant Handled
Sulfuric acid makers	Nitrous gases and nitric acid
	Sulfuric acid
Sulfuric acid workers	Arsenic
Surgical dressing makers	Phenol
Table makers	Manchineel
Tallow refiners	Acrolein
	Carbon disulfide
	Sulfuric acid
Tannery workers	Ammonia
	Amyl acetate
	Aniline
	Arsenic
	Benzine
	Chloride of lime
	Cyanogen compounds
	Formaldehyde
	Formic acid
	Hydrochloric acid
	Mercury and its compounds
	Oxalic acid
	Sodium hydroxide
	Sulfuric acid
Tapers (airplanes)	Tetrachlorethane
Tar distillery workers	Cresol
Tar workers	Tar
Taxidermists	Arsenic
	Mercury
Tear gas makers	Bromine
	Chlorine
Tear gas makers (chloropicrin, trichlornitromethane)	Picric acid (trinitrophenol U.S.P.)
Temperers	Cyanogen compounds
	Petroleum
	Sulfuric acid
Tetra-ethyl lead makers	Bromine
Textile printers	Formaldehyde
Thallium workers	Thallium
Thermometer makers	Mercury
	Thallium
Thinners	Acrolein
	Ammonia
	Arsenic
	Hydrochloric acid
Tool handle makers	Coco-bolo
Tower men (sulfuric acid)	Nitrous gases and nitric acid
	Sulfuric acid
Toy makers	Amyl acetate
	Arsenic
	Yew tree
Transfer workers (pottery)	Turpentine
Transparent wrapping material workers	Acetone
	Carbon disulfide
	Hydrochloric acid
	Sodium hydroxide
	Sulfuric acid
Treaders (rubber)	Benzene
Tree sprayers	Cyanogen compounds
Trinitrotoluene makers	Benzene
	Nitro-aniline
Turnery	African ebony
	Brigalow spearwood
	Canoe birch
	Ground juniper
	Indian jungle wood
	Laburnum
	Molucca ebony
	Lemon wood
	Sabicu
	South African boxwood
	Surinam greenheart
	Walnut
	West Indian satinwood
	Yew tree
Turpentine extractors	Turpentine
Type cleaners	Benzine
	Methanol (methyl alcohol)
Type founders	Antimony
Type melters	Acrolein
Umbrella handle makers	Snakewood
	Tonca bean
Upholsterers	Methanol (methyl alcohol)

Occupation	Irritant Handled
Varnish makers	Acetone
	Acrolein
	Ammonia
	Amyl acetate
	Aniline
	Benzine
	Benzene
	Butyl alcohol
	Formaldehyde
	Methanol (methyl alcohol)
	Tetrachlorethane
	Turpentine
Varnishers	Acetone
	Amyl acetate
	Amyl alcohol
	Aniline
	Benzine
	Benzene
	Butyl alcohol
	Formic acid
	Methanol (methyl alcohol)
	Tetrachlorethane
	Turpentine
Vehicle makers	Brauna
	Surinam greenheart
Velvet makers	Arsenic
Veneerers in sleeping cars	Tonca bean
Veneer makers	Common alder
	East Indian satinwood
	Macassar wood
	Sand-box tree
Vignetters	Hydrochloric acid
Violin parts makers	Turkish boxwood
Vulcanizers	Aniline
	Antimony
	Benzine
	Benzene
	Carbon dioxide
	Carbon disulfide
	Carbon tetrachloride
	Chromium compounds
	Methanol (methyl alcohol)
Wainscoting	Manchineel
Wallpaper printers	Arsenic
	Chromium compounds
Watch gilders	Mercury
Waterproof cloth makers	Benzine
Waterproof fabric makers	Benzene
Waterproofers (paper)	Formaldehyde
Waterproofers (paper and textile)	Chromium compounds
Wax ornament makers	Arsenic
Wax ornament workers	Chromium
Wax refiners	Sulfuric acid
Welders	Benzene
	Mercury
Wheel makers	Fustic
Window shade makers	Benzine
	Benzene
Wire drawers	Arsenic
	Sulfuric acid
Wire makers	Hydrochloric acid
Wirers (incandescent lamps)	Amyl acetate
Wood (methyl) alcohol distillers	Acetone
	Methanol (methyl alcohol)
Wood polishers	Chromium compounds
Wood preservers	Arsenic
	Mercury
	Phenol
	Tar
Wood stainers	Chromium compounds
Wood workers	Benzine
	Methanol (methyl alcohol)
Wringers (guncotton)	Nitrous gases and nitric acid
Yeast makers	Sulfuric acid
Zinc chloride makers	Chlorine
	Hydrochloric acid
Zinc electrode makers	Mercury
Zinc miners	Arsenic
Zinc refiners	Arsenic
	Antimony
Zincers	Cyanogen compounds

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NECROBIOSIS LIPOIDICA DIABETICORUM

REPORT OF A CASE WITH CLINICAL, PATHOLOGIC AND BIOCHEMICAL OBSERVATIONS

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According to a recent review of the literature,[1] necrobiosis lipoidica diabeticorum is a rare condition; the case to be reported here is the fifteenth. This low incidence, however, may be more apparent than real; there is reason to suspect that with improvement in diagnosis the incidence will be found to be greater than that recognized at present. One of us (I. M. R.) has the impression that in the past the condition was overlooked among his own cases of diabetes, and Joslin [2] expressed the same opinion; at the time he made the statement there were six patients with suspected necrobiosis lipoidica diabeticorum in one clinic in Boston. However, these are clinical impressions only; according to histologic studies there is still reason to believe that the condition is rare.

The clinical appearance of necrobiosis lipoidica diabeticorum and the histologic picture, according to the extent, the stage and the duration of the lesion, are now well known. Early lesions generally appear as uniform round, oval or irregularly shaped, firm papules, with a red or bluish violet border and a yellowish center. In the earliest stages the lesions are not unlike xanthoma. A careful examination, however, shows that though the center of the lesion is yellow, the periphery, unlike that of a xanthoma, has a violet hue. As the lesion progresses, it tends to increase in size and to lose its papular character. The older lesions also tend to be more irregular; the border becomes reddish brown, and there is a tendency toward atrophy at the center. The surface in time becomes scaly, and the thin epidermis is traversed by telangiectatic vessels. The pigmentation appears to depend largely on the type and amount of lipoid deposited in the connective tissue, the degree of circulatory stasis and the amount of hemosiderin present. Unlike xanthoma, the condition has

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1. Zeisler, E. P., and Caro, M. R.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **30**:796 (Dec.) 1934.
2. Joslin: Personal communication.

not been found in nondiabetic persons, and though the sites commonly involved are the dependent portions of the body—chiefly the regions below the knees—lesions have been found on the trunk and elsewhere. Ulceration may occur. Unlike xanthoma, necrobiosis lipoidica diabeticorum does not as a rule respond to treatment. Cicatrization has been noted. The condition is to be differentiated chiefly from xanthoma, extracellular cholesterosis of Urbach, localized amyloidosis, localized scleroderma, erythema induratum, acrodermatitis chronica atrophicans and localized myxedema.

Histologically, necrobiosis lipoidica diabeticorum is essentially a lesion of the corium, with swelling of the fibers of collagen, inflammation and thickening of the deeper vessels with thrombosis which leads to necrosis, and deposition in the necrotic areas of particles of fat. Polariscopic examination has failed to reveal any double refraction. The deposits of hemosiderin appear, as stated, to be due to stasis. Histologically, necrobiosis lipoidica diabeticorum is readily differentiated from xanthoma tuberosum by the presence in the latter of the characteristic foam cells. Its occurrence in diabetic persons only, its resistance to dietetic treatment and insulin and its histologic characteristics readily differentiate it from xanthoma, the condition which it most closely resembles.

A number of theories have been suggested as to the mechanism of the production of necrobiosis lipoidica diabeticorum. Since it has been generally found to occur in association with lipemia, the consensus is that it is an intense vasculitis aggravated by fatty infiltration due to the circulating blood lipoids. More details of the clinical and the pathologic picture are given in the excellent review by Zeisler and Caro.[1]

REPORT OF CASE

A man aged 25 had diabetes for nine years. Because he cooperated poorly the disease had rarely been well controlled; glycosuria and hyperglycemia had been present as a rule; ketosis had been a frequent finding, and there had been a number of attacks of acidosis. Prior to 1930, when the diet was low in carbohydrates and high in fat, hyperlipemia was a fairly constant finding, cholesterol values of 0.3 per cent or more being observed. Late in 1930, when the diet was changed to a high carbohydrate and low calory regimen, the cholesterol content of the blood decreased, and since then it had ranged between 0.12 and 0.22 per cent.

The first cutaneous lesion was noted early in 1930, when the diet was still low in carbohydrate and high in fat. It appeared as a small elevated papule below the left knee. During the following eight months similar lesions appeared on the left arm and on both ankles. Eventually all the lesions lost their papular character, and the flattened surfaces became scaly. No lesion disappeared entirely. In August 1934 the patient was referred from the clinic for persons with diabetes to the clinic for patients with cutaneous diseases. According to the note made at that time the condition was as follows:

The skin was normal, except for four plaques, the largest of which was over the left knee and was about 1 inch (2.5 cm.) in diameter. There was a slightly

smaller lesion on the left arm below the shoulder. The two smallest lesions were on the external malleoli. The plaques were from circular to oval, and each was sharply defined from surrounding skin. The surface of the lesions, depressed below the level of the skin, was smooth, glistening and ramified with telangiectatic vessels. On the lesions were also a number of scales, ranging in size from that of a pinhead to about 0.3 cm. Removal of the scales left depressions. The lesions appeared waxy and were yellowish violet, deepening to a darker violet at the periphery. Under pressure with the diascope the yellow color seen through the glass was distinct. On palpation the plaques were firm, not unlike those of morphea.

The plaque below the knee was removed in its entirety for histologic and biochemical examination. For control observations a similar amount of apparently healthy skin was removed from the same extremity, some distance from the lesion.

Fig. 1.—Appearance of nodule on skin below the knee.

Pathologic Report (Dr. L. J. Rhea).—Sections embedded in paraffin were stained with hematoxylin and eosin, with Van Gieson's stain for collagen and with Weigert's stain for elastic tissue. Frozen sections were stained with scarlet red for detection of lipoids.

The stratum corneum was slightly thickened. The stratum granulosum was intact. There was flattening at the site of the papillae, and the epidermis was thinned throughout the section. The changes of particular interest were in the corium. There were several areas of necrobiosis in which the collagen appeared pale and homogeneous and in which there was absence of nuclei, although for the most part the fibrillar structure of the cells was intact. Toward the periphery of these foci the collagen fibers appeared more normal in architecture and retention of nuclei, although the edema was marked. Surrounding these necrobiotic foci there were collections of cells, which in some areas consisted chiefly of lymphocytes, and in others of fibroblasts. In the latter areas the fibroblasts were seen to extend into the necrobiotic foci, the extension suggesting some attempt at repair. There was perivascular infiltration, and in areas of infiltration the vessels

had a thickened proliferating intima, even to the point of occlusion of the lumens. No massive necrosis was seen. Between the foci, the collagen appeared normal. The elastic fibers were absent in the center of the foci and broken up toward the periphery. Frozen sections stained with scarlet red showed that the largest deposits of granules of fat occurred in the necrobiotic foci. The granules were brownish red, whereas the neutral fat was brilliant orange red. In these foci, the globules of fat, which were of varying size, were chiefly extracellular with some fine intracellular droplets. Toward the periphery there was a lesser infiltration of lipoid material, and some of it was seen in the fibroblastic cells in the form of fine droplets. Droplets were also observed in the focal infiltrate and in the walls of the vessels. Extracellular globules were also noted between the normal collagen fibers outside the affected sites. No amyloid, calcium or hyalin was noted.

Fig. 2.—Low power photomicrograph of section from the lesion shown in figure 1.

Chemical Analysis.—Preparation of Materials: The samples of skin, while fresh, were carefully freed of subcutaneous fat, finely minced with sharp scissors and weighed. The lipids were then extracted repeatedly with Bloor's mixture of alcohol and ether. At each extraction the mixture was brought to the boiling point, kept boiling for several minutes and then filtered through dry filter paper. Bloor's mixture was used in preference to other preparations since the extract obtained by the use of that mixture lends itself more readily to the methods used for analysis of lipoids.

This method of extraction is not strictly quantitative but, as the data show, is sufficiently so for the present purposes. To test the thoroughness of the extraction, the residues of the samples of skin were dried to constant weight and then sub-

jected to extraction with dehydrated alcohol, chloroform and absolute ether. The residues were then subjected to the hydrolytic action of sodium hydroxide, acidified and finally extracted with purified petroleum benzine as described by Eckstein and Wile.[3] The results of the double extraction are shown in table 1. It will be observed that in extractions made according to the more elaborate method of Eckstein and Wile the additional recovery of lipoid material was less than 10 per cent of the total.

Method of Analysis: The amounts of free cholesterol and cholesterol esters were determined by the method of Bloor and Knudson.[4] Whitehorn's [5] method was used with slight modification for determination of the phospholipoid fraction. The results are shown in table 2.

TABLE 1.—*Results of Alcohol-Ether Extraction of Skin*

	Lesion, Grams	Control Skin, Grams
Weight of original sample	0.8340	1.1200
Weight of alcohol-ether extract	0.0693	0.0365
Weight of Eckstein-Wile extract*	0.0044	0.0029

* These figures represent the weight of residue after removal of alcohol-ether extract.

TABLE 2.—*Results of Analysis of Lesion and Apparently Healthy Skin of the Same Extremity*

	Lesion	Control Skin
Total lipoids		
Percentage of total material	8.31*	3.260*
Cholesterol		
Percentage of total material	2.21	0.520
Percentage of total lipoids	26.50	15.800
Free cholesterol		
Percentage of total material	2.02	0.450
Percentage of total lipoids	24.30	13.800
Percentage of total cholesterol	91.40	86,500
Cholesterol esters		
Percentage of total material	0.19	0.070
Percentage of total lipoids	2.28	2.150
Percentage of total cholesterol	8.60	13.500
Phospholipoids		
Percentage of total material	0.24	0.061
Percentage of total lipoids	2.80	1.800

* All the values are expressed as percentage of original skin.

COMMENT

Interpretation of the observations in this case is difficult because of the scantiness of data on analysis of skin in general. In Wells' "Chemical

3. Eckstein, H. C., and Wile, U. J.: The Cholesterol and Phospholipoid Content of the Cutaneous Epithelium in Man, J. Biol. Chem. **69**:181, 1926.

4. Bloor, W. R., and Knudson, A.: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J. Biol. Chem. **27**:107, 1916.

5. Whitehorn, J. C.: A Method for the Determination of Lipoid Phosphorus in Blood and Plasma, J. Biol. Chem. **62**:133, 1924.

Pathology,"[6] for example, skin is not even indexed. The data collected by Michelson and Laymon[7] are based on histochemical (staining) properties, and it is well known that even when as much as 2 per cent of fat is present it may be difficult to stain normal skin with the usual stains for fat. Channon and Harrison[8] and Eckstein[9] have reported the results of analysis of subcutaneous fat. The data of Eckstein and Wile[10] and of Wile, Cameron and Eckstein[11] refer to cutaneous epithelium only, and the analyses of normal skin which we have found[12] and which, it is assumed, included observations on corium and epithelium were made on postmortem material; moreover, there was no mention of the causes of death, of the time which had elapsed between death and the collection of the material or of precautions taken to exclude subcutaneous fat. The importance of excluding subcutaneous fat is clearly seen in experiences with cholesterol. Unna and Golodetz,[13] for example, found as much as 16 per cent of sterol in the lipoids of the outer layers of the skin. Eckstein and Wile[8] also observed a high sterol content in cutaneous epithelium in their two samples, the cholesterol content amounting to 24.1 and 19.9 per cent of the total lipoids, respectively, whereas, Eckstein[9] found that in subcutaneous fat the cholesterol content was only 0.24 per cent of the total lipoids. Interpretation of the available data is still further complicated by the different technical procedures used.

The total lipoid content of the apparently healthy skin in the case reported here, namely, 3.26 per cent of the total amount of skin, does not appear to be excessive. In Urbach's[12b] collection of data there is a report of one analysis of normal skin, and the value for lipoids is much lower, namely, 0.97 per cent of the total amount. Harrison[12a] found the percentage of lipoids to be 4.4. As stated, however, these data are

6. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

7. Michelson, H. E., and Laymon, C. W.: Necrobiosis Lipoidica Diabeticorum, J. A. M. A. **103**:163 (July 21) 1934.

8. Channon, H. J., and Harrison, G. A.: The Chemical Nature of the Subcutaneous Fat in the Normal and Sclerematous Infant, Biochem. J. **20**:84, 1926.

9. Eckstein, H. C.: The Fatty Acids in the Subcutaneous Fat in Man, J. Biol. Chem. **64**:797, 1925.

10. Eckstein, H. C., and Wile, U. J.: The Cholesterol Content of the Cutaneous Epithelium of Man, J. Biol. Chem. **67**:lix, 1926; footnote 3.

11. Wile, U. J.; Cameron, O. J., and Eckstein, H. C.: Effect of the Roentgen Rays on the Lipoids of the Epidermis, Arch. Dermat. & Syph. **32**:69 (July) 1935.

12. (*a*) Harrison, G. A.: Chemical Methods in Clinical Medicine, London, J. & A. Churchill, 1930. (*b*) Urbach, E.: Lipoidstoffwechselerkrankung, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 12, p. 328.

13. Unna, P. G., and Golodetz, L.: Die Hautfette, Biochem. Ztschr. **20**:469, 1909.

not strictly comparable with our own since they were obtained on material from cadavers. That the amount is excessive is, however, suggested by data obtained with cutaneous epithelium. Eckstein and Wile [3] reported that 2.4 and 3.8 per cent of lipoids, respectively, was contained in skin from two cadavers. Much higher values were obtained in cases of exfoliative dermatitis; the amounts ranged between 6.9 and 8.2 per cent. The tissues, however, were not healthy. Zeisler and Caro [1] found the lipoid content to be 6.21 per cent. In a recent study of the effects of roentgen rays on the lipoids of epidermis, Wile, Cameron and Eckstein [11] found that the total lipoid content ranged between 1.11 and 2.13 per cent. Their determinations were also made on postmortem material, but the tissues were obtained within a few hours after death. From the combined data, therefore, it appears that the greater part of the lipoids of the skin, excluding subcutaneous tissue, is in epidermis. Therefore, since in our case corium was included in the tissue analyzed, it appears reasonable to conclude that the lipoid content of the skin was greater than normal even in the apparently healthy tissue. In the necrobiotic tissue the total lipoid content was definitely increased, the content being 8.31 per cent, and thus the observations corresponded to the values recorded in general for xanthomatous tumors.[14] Determination of the total lipoid content of skin, therefore, appears to be of no value in differentiating the lesions of necrobiosis lipoidica diabeticorum from those of xanthoma, which they resemble closely clinically.

The total cholesterol content in the case reported here amounted to 15.8 per cent of the total lipoids of the apparently healthy skin and to 26.5 per cent of the material from the lesion. There was much more cholesterol in the material from the lesion; the apparently healthy skin contained 0.52 per cent, whereas, the lesion contained 2.21 per cent cholesterol. In their analysis Zeisler and Caro [1] found that the cholesterol content was 8.9 per cent of the total lipoids. None of the observations differs from those reported in cases of xanthoma. Determination of the total cholesterol content, therefore, also appears to be of no value for the purposes of differential diagnosis.

Determination of free cholesterol and cholesterol esters appears to be of diagnostic value. Zeisler and Caro [1] did not record their observations for the two forms of cholesterol separately. It will be observed that in our case the amount of free cholesterol was 91.4 per cent of the total cholesterol in the necrobiotic tissue and 86.5 per cent in the apparently healthy tissue. The observations on the healthy skin agree with the data of other workers for normal skin. The high percentage

14. (*a*) Wile, U. J.; Eckstein, H. C., and Curtis, A. C.: Lipid Studies in Xanthoma, Arch. Dermat. & Syph. **19**:35 (Jan.) 1929. (*b*) Michael, J. C., and Nicholas, H. O.: Blood Lipids in Xanthoma, ibid. **29**:228 (Feb.) 1934. (*c*) Harrison.[12a]

of free cholesterol in the necrobiotic tissue, however, appears to differentiate necrobiosis lipoidica diabeticorum from xanthoma; in the latter, the greater part of cholesterol has been found combined as an ester; Michael and Nicholas,[14b] for example, found that cholesterol esters amounted to 87.8 per cent of the total cholesterol.

The amount of phospholipoids also appears to differentiate necrobiosis lipoidica diabeticorum from xanthoma. In the case of Michael and Nicholas [14b] the amount of phospholipoids was 31.3 per cent of the total lipoids, whereas, in our case it was only 2.8 per cent and corresponded closely with the value found in the apparently healthy skin and with that reported for normal skin. Zeisler and Caro [1] in their case of necrobiosis lipoidica diabeticorum found that the amount of phospholipoids was a small portion of the total lipoid content.

It appears that the biochemical observations in necrobiosis lipoidica diabeticorum are not unlike those in xanthoma with respect to total lipoid and total cholesterol content. In both conditions the values, as calculated on material from lesions, are definitely above normal. It appears, however, that necrobiosis lipoidica differs from xanthoma with respect to relative proportions of free cholesterol and cholesterol esters and to percentage of lipoids in the form of phospholipoids. In the interpretation of the data, however, consideration should be given to the possibility that the observations may not be characteristic for necrobiosis lipoidica diabeticorum but may be related to the stage of the lesion and the metabolism of the patient in general. Our case, therefore, is reported for purposes of record only. It should here be observed that in the only case of extracellular cholesterosis in which chemical analyses were made the total cholesterol content of the nodule was five times that of normal tissue; that of the apparently normal skin was twice the normal amount, and the proportion of free to total cholesterol was also higher than in xanthoma.[15] The literature and the experiences in the case reported here clearly emphasize the necessity of control data, and not least important are the analyses of skin of perfectly normal persons obtained during life. This phase of the subject is now being investigated.

15. Urbach, E.; Epstein, E., and Lorenz, K.: Arch. f. Dermat. u. Syph. **166:** 243, 1932.

CALCIUM METABOLISM IN SCLERODERMA

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Scleroderma, like many other poorly understood diseases, has been ascribed to numerous causes. According to the peculiar experience or view of the observer, trauma, infection and physical agents have been suggested as etiologic factors in scleroderma. Some investigators have incriminated the nervous system and others the endocrine glands, while still others have expressed the belief that combinations of some or all of these factors are necessary to precipitate the disease. Either such varied theories as to the etiology obscure the true cause of scleroderma or the disease is a symptom complex which can be produced by more than one agent. If many excitants can give rise to scleroderma, it would be useful to find some constant characteristic of this symptom complex. There is increasing evidence that at least one finding is consistently associated with scleroderma, namely, disturbance of calcium metabolism. The association is fairly obvious when scleroderma occurs together with calcinosis, as in the Thibierge-Weissenbach syndrome. In 1919 Jadassohn [1] showed by histologic methods that calcium is deposited diffusely in the corium between the collagen fibrils, an observation which has been confirmed [2] by chemical analyses, which show that sclerodermatous skin contains more calcium than normal skin. Our own observations confirm this observation.

Only relatively recently has the relationship between calcium metabolism and the parathyroid glands been established. Because of the occurrence of calcium deposits in scleroderma the parathyroid glands have been implicated by certain investigators. For example, Bernheim and Garlock [3] attached primary significance to the parathyroid glands. They

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1. Jadassohn, J.: Arch. f. Dermat. u. Syph. **126**:172, 1919.
2. Leriche, R., and Jung, A.: Bull. Soc. franç. de dermat. et syph. **42**:885, 1935.
3. Bernheim, Alice R., and Garlock, John H.: Ann. Surg. **101**:1012, 1935.

expressed the belief that prolonged deficiency of calcium intake leads to overfunction of the parathyroid glands, which in turn is conducive to, or directly produces, scleroderma, among other disorders. They said that prolonged deficiency of calcium intake finally exhausts the body stores and that as a result the parathyroid glands become hyperplastic. Thus the conclusion was reached that hyperparathyroidism is the immediate cause of scleroderma. The recent work of Selye [4] supports this. He has been able to produce scleroderma-like lesions in young rats by injections of parathyroid extract, but he has emphasized the fact that such lesions can be produced only in very young rats. In older rats it has been impossible to produce the lesions. It should be remarked here, however, that rats have been found to be relatively refractory to the action of parathyroid extracts.

Sannicandro [5] expressed the belief that scleroderma is due to dysparathyroidism but did not specify whether it is hyperfunction or hypofunction of the glands which is responsible for the disorder. He has found that certain patients improve as a result of administration of parathyroid extract. He expressed the belief that it is impossible to distinguish clinically between scleroderma due to hyperparathyroidism and that due to hypoparathyroidism, and he concluded that any deviation from the normal function of the parathyroid glands may lead to scleroderma.

A third point of view may be mentioned, namely, that of Sellei,[6] who stated that scleroderma is a "dysfermentosis" and that the "dysfermentosis" induces anatomic or physiologic changes in certain of the endocrine glands. His treatment, based on this theory, involves the use of organ extracts and is reported by him to be successful.

There are recorded in the literature a number of cases of scleroderma in which partial parathyroidectomy was performed. It would be impracticable to list all of them here. Of the investigators who have reported on this procedure, Leriche [7] is perhaps most prominent, because of his priority in the field and the number of patients he has studied. In general, his reports have been favorable. He expressed the belief that a change occurs in the parathyroid glands and that this is followed by withdrawal of calcium from the bones. Atrophy of the skin then occurs.

Puddu [8] listed a case of scleroderma which he studied as well as sixteen others, not his own, reported in the literature. Surgical

4. Selye, H.: Condition Simulating Human Scleroderma in Rats Injected with Parathyroid Hormone, J. A. M. A. **99**:108 (July 9) 1932.

5. Sannicandro, Guiseppi: Arch. ital. di dermat., sif. **11**:88, 1935.

6. Sellei, Joseph: Arch. f. Dermat. u. Syph. **171**:577, 1935.

7. Leriche, R., and Jung, A.: Presse méd. **43**:1361, 1935.

8. Puddu, Vittorio: Policlinico (sez. prat.) **41**:1801, 1934.

removal of a portion of the parathyroid glands in thirteen cases gave variable results. Apparently all the patients experienced an immediate relief, which continued for a time, the period differing with each patient. In a few patients there was gradual relapse to the preoperative condition, while in the great majority the condition became stationary. Some experienced a stormy period of readjustment after the operation; others had an uneventful recovery.

It may be concluded from the results of the various observers that one may expect a partial, although frequently transitory, improvement of the scleroderma after partial parathyroidectomy, and it must be granted that this fact is strong evidence that the condition is due to hyperfunction of the glands. There are, however, several reasons for questioning the logic involved. One may ask, for example, why there is only partial improvement after parathyroidectomy. We are aware that there is the possibility of an irreversible change having occurred in the sclerodermatous skin. Apparently this is not true in the early stages of the disease, however, since there is occasionally spontaneous involution to the normal state. Moreover, if scleroderma were due only to hyperparathyroidism, relief of the latter should lead to a cure of scleroderma, leaving only such destruction as had already taken place. Induction of hypoparathyroidism does not do this. It leaves part or all of the scleroderma. The remaining dermatosis cannot be said to be due to hyperparathyroidism.

In certain patients with scleroderma adenoma of the parathyroid glands has been found; in others there was definite hyperplasia. In the majority of patients, however, the glands appeared normal. The results after resection of the adenomas or hyperplastic glands were no better than the results obtained after removal of apparently normal glands. Ssamarin [9] has reported several cases in which tissue removed at operation was shown by microscopic examination not to be parathyroid tissue and yet the patient experienced results equal to those in patients from whom actual parathyroid tissue was removed. This is strong evidence that parathyroidectomy per se is not responsible for whatever relief is obtained. Possibly trauma in the region of the thyroid or the mental and physical rest involved may be regarded as the cause of the improvement.

One of the principal (and almost invariable) observations in true hyperparathyroidism is hypercalcemia associated with hypophosphatemia. In scleroderma there is frequently a slight elevation of the calcium content of the blood. On the other hand, normal values are found about as often, and several cases have been recorded in which the calcium content of the blood was definitely below normal. Further, in scleroderma the

9. Ssamarin, N. N.: Arch. f. klin. Chir. **153**:358, 1928.

amount of phosphorus in the blood is usually normal, or when it is abnormal is almost invariably elevated rather than decreased, as one would expect in true hyperparathyroidism.

Another observation in hyperparathyroidism is that of hypercalciuria. The few authors who have studied the calcium content of the urine in cases of scleroderma have reported a markedly decreased urinary output of calcium. This is in agreement with our results.

Possibly the commonest finding in hyperparathyroidism is the negative calcium balance: More calcium is excreted than is ingested in any given period. The only observations on the calcium balance in scleroderma which we have been able to find in the literature are those of Paggi [10] and of Brooks.[11] Paggi found a positive balance, which suggests hyperparathyroidism if the intake is normal. Paggi ligated three of the thyroid arteries in his patient; after this there was a short period of improvement. The clinical response was negative. The calcium balance had become slightly negative fifty days after the operation. Paggi's results, however, are open to the criticism that the study was made only for single short periods before and after the operation. Observations made during one or two widely separated five day periods may not represent a true picture of the metabolism over long periods.

Brooks reported on the calcium balance in scleroderma with and without calcinosis. He found that there was retention of calcium in calcinosis but not in ordinary scleroderma. His results, like those of Paggi, may be criticized because the periods of observation were short and the study was not carried out over a long enough period. It is not clear from his report how he determined the calcium intake. If it was estimated by weighing the food and calculating the calcium content from tables, his results are open to further criticism. We have found that the result of chemical determination of the calcium content of food differs by as much as 20 per cent from the value estimated from tables. We believe, therefore, that results of studies of calcium balance without accurate determination of the calcium content of the food are not reliable. Brooks fed his patients diets low in calcium in an attempt to produce a large negative balance. His results, then, can hardly be regarded as characteristic of patients on normal diets and are not, therefore, comparable with ours.

We present the results of our studies, including studies of the calcium and phosphorus balance on two patients. These balance studies were conducted over long periods and are, we believe, free from the aforementioned criticisms.

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10. Paggi, Bruno: Policlinico (sez. chir.) **41**:371, 1934.
11. Brooks, W. D. W.: Quart. J. Med. **3**:293, 1934.

In the two patients on whom balance studies were made there was unquestionably definite retention of both calcium and phosphorus beyond the amount conceivably necessary for growth of bone. Probably much of the retained calcium was deposited in the skin and muscular tissue. The disturbance of calcium metabolism may be so severe in some cases as to cause transfer of calcium from the fixed stores of the body—the bones—to the soft tissues, although this was apparently not the case in the two patients on whom the balance studies reported here were made. We do not wish to state on the basis of the studies on two patients presented here that all patients with scleroderma show retention of calcium and phosphorus, but when all facts are considered it seems reasonable to believe that retention of calcium may be a fairly general feature of the condition. Certainly all investigators seem to agree that the calcium metabolism is affected.

At present, however, in view of the conflicting nature of the reports in the literature, nothing definite can be said as to the cause of this perversion of the calcium metabolism. Indeed, it is not known whether the disturbed calcium metabolism is the cause of the symptoms or whether the reverse is true, for there are apparently a preliminary hypertrophy and hyperplasia of the collagen tissue of the skin. Conceivably this condition may be caused by some unknown factor and in turn may lead to deposition of calcium. The factors controlling the deposition of mineral in the soft tissues of the body are not fully known. We do not feel that it has been proved that parathyroid dysfunction is the underlying cause of scleroderma. Nor has there been any indication in the results of our studies or of those of others that there has been either a deficiency or an excess of vitamin D or any other factor known to influence mineral metabolism in any of the patients.

It has been shown repeatedly that massive doses of vitamin D cause loss of calcium, which may or may not be accompanied by hypercalcemia. The source of the calcium thus lost from the body has been assumed, with some justice, to be the fixed stores of the body, although no proof of this has been offered.

It seemed to be of interest, therefore, both from a practical and from a theoretical point of view, to administer large amounts of vitamin D to subjects in whom there was abnormal deposition of calcium in soft tissues, in an effort to determine whether such abnormal calcium might not be removed before the normal fixed stores were depleted.

METHODS

The patients were brought to the hospital, and after three or four days the study was started. All urine and feces were collected for each twenty-four hour period; all food was weighed, and duplicate samples were sent, with the excreta, to the

laboratory for analysis. The nurses, attendants and patients received careful instruction and supervision in the collection of the specimens for analysis to insure collection of true daily samples.

A duplicate of the food for each day was placed in weighed containers and dried in ovens at a temperature of from 140 to 150 C. After the material had been dried the contents were weighed and ground to fine powder, and all the food for one metabolic period was combined and thoroughly mixed. A sample of this mixture was then used for analysis for calcium and phosphorus. The feces were treated in exactly the same manner. The urine excreted each day was mixed and

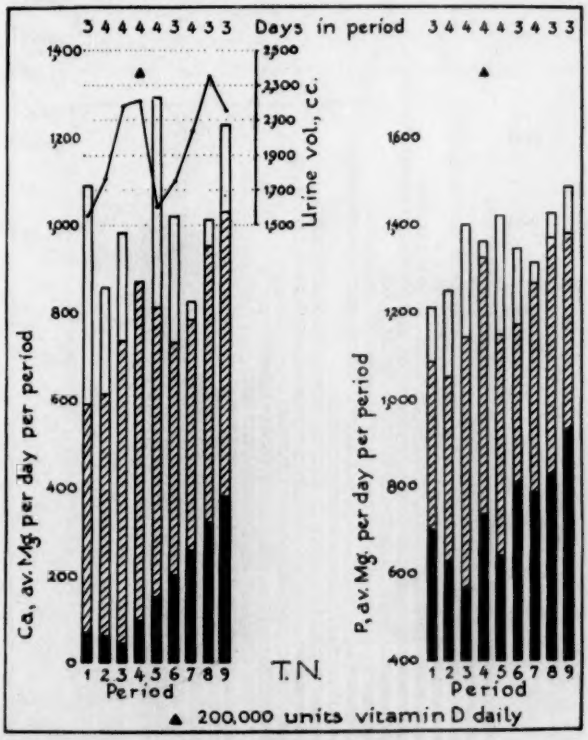
3 4 4 4 4 3 4 3 3 Days in period 3 4 4 4 4 3 4 3 3
Urine vol., c.c.
Ca, av. Mg per day per period
P, av. Mg. per day per period
Period
Period
T.N.
▲ 200,000 units vitamin D daily

Chart 1 (case 1).—Graph showing results of study of calcium and phosphorus balance beginning on Aug. 29 and ending on Sept. 29, 1935. In this and in the following charts the black area represents urinary excretion, the single cross hatch area indicates fecal excretion, the double cross hatch area shows excess of total excretion over intake and the white area represents excess of intake over total excretion.

measured, and one tenth of the output was saved and mixed with one tenth of the output for each day in the period. An aliquot portion of this mixture was then used for analysis.

Samples of dried food, of dried feces and of urine were ashed in platinum dishes over Meker burners, and the ash was dissolved in half-normal hydrochloric acid. The solution was made to exactly 200 cc., and aliquot portions were used to determine the calcium and phosphorus content. From these results the average

daily intake and output for the period were calculated, and the balance was expressed in milligrams per day of calcium and phosphorus retained or lost. The chemical methods used were slight modifications of the method of Shohl and Pedley [12] for calcium and of the method of Pincus [13] for phosphorus.

REPORT OF CASES

CASE 1.—T. N., a man aged 55, had generalized scleroderma for six years. The hands and face were first affected; then other parts of the extremities as well as

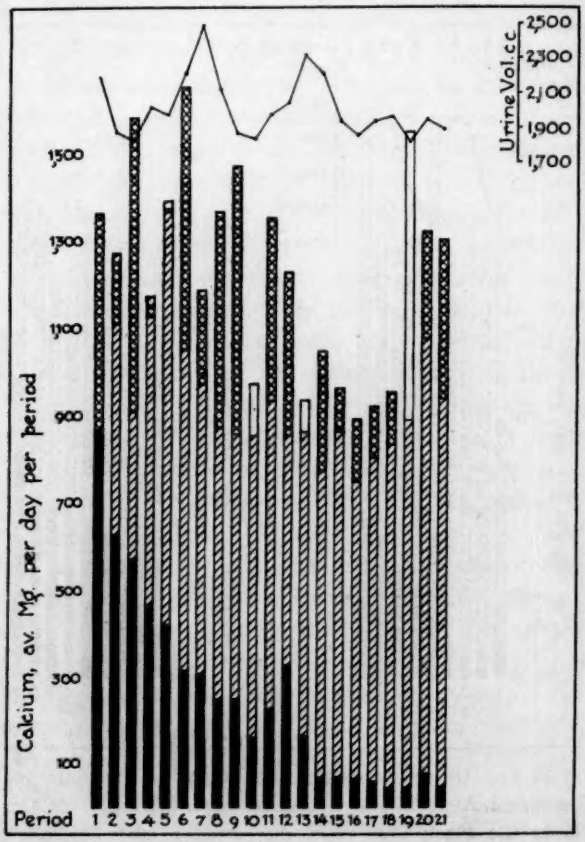

Chart 2 (case 1).—Graph showing results of study of calcium balance beginning on May 16 and ending on Aug. 26, 1936.

the neck and trunk became involved. He had received various treatments with more or less improvement, the greatest benefit being derived from typhoid vaccine. He first came under our observation in August 1935. At that time he came into the hospital and was placed in the ward for patients with metabolic disorders for

12. Shohl, A. T., and Pedley, F. G.: J. Biol. Chem. **50**:537, 1922.
13. Pincus, S.: Virchows Arch. f. path. Anat. **16**:137, 1859.

studies of calcium and phosphorus balance. The results are shown in figure 1. He showed marked retention of both calcium and phosphorus and a low calcium content of the urine. After three metabolic periods, administration of 200,000 U. S. P. units of vitamin D daily in the form of viosterol[14] was begun. Within three weeks after the administration of vitamin D the calcium content of the urine had risen over 300 per cent, or to the upper limits of the normal range. The balance remained positive, although to a less degree, except in the last period, when the intake was unusually large. The patient continued to take vitamin D at home for the following seven and a half months. Approximately two and a half months after administration of vitamin D was instituted definite improvement was noticed in his condition. All parts except the hands had softened somewhat. After eight months only slight induration remained in the affected parts except in the skin over the hands. There was, however, enough improvement to permit flexion of the

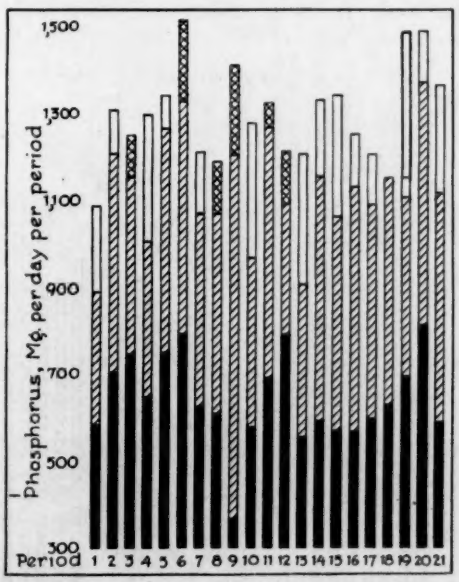

Chart 3 (case 1).—Graph showing results of study of phosphorus balance beginning on May 16 and ending on Aug. 26, 1936.

hands, an action which had been impossible since the onset of the disease. At this time all medication was discontinued, and the patient was again admitted to the hospital for further balance study. The results are shown in figures 2 and 3. The study was carried on for one hundred and five days, and during the entire time there was a negative balance and no indication of a return to a positive balance. At the time of writing the condition continues to improve. Roentgen studies of the bone at no time showed rarefaction.

Case 2.—C. K., a girl aged 20, injured her hand and shortly after the accident noticed induration of the skin over the hands. This hardness spread and became

14. The vitamin D solution used in these studies contained approximately 1,000,000 U. S. P. units per gram of solution; it was furnished by Mead Johnson & Co.

generalized. She came under our care three years later, with general scleroderma and marked sclerodactyly. She was admitted to the hospital for studies of calcium and phosphorus balance and was found to have a positive balance, retaining large quantities of calcium and phosphorus (fig. 4). After three periods, administration of 200,000 U. S. P. units of vitamin D daily was instituted. Again, as in case 1, the calcium content of the urine rose from a low value to a normal or higher value; the calcium content of the feces remained unchanged. An unusually large intake during the last period is probably the reason for the balance remaining positive. The patient was discharged from the hospital but the treatment was continued at home. After three months there was appreciable improvement in her clinical

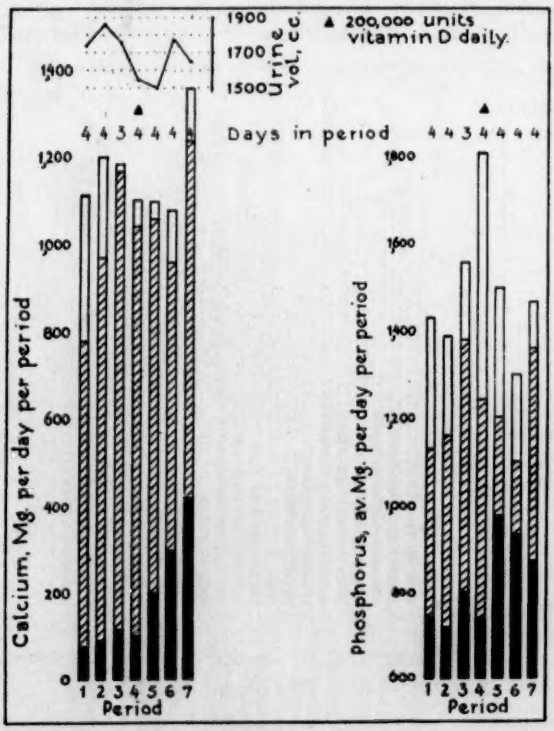

Chart 4 (case 2).—Graph showing results of study of calcium and phosphorus balance on first admission to the hospital. The study was started on July 2 and ended on July 28, 1935.

condition, except in the hands. After five months all involved areas had improved considerably, although improvement in the hands was less than in other areas. Nevertheless, she could clench her hands for the first time since the onset of her illness. At this time the right inferior parathyroid gland was resected, and the treatment with vitamin D was interrupted for a month. Section of the gland showed moderate infiltration of fat. Two months later the appendix was removed, the patient making an uneventful recovery. Eight months after the first balance study she returned to the hospital for further observation, the results of which are shown in figures 5 and 6. Administration of vitamin D was stopped when the

patient was readmitted to the hospital. The balance remained consistently negative throughout her stay in the hospital, and there was no indication of a tendency to a return to a positive balance, even when the intake was reduced. Unfortunately the patient would not stay in the hospital sufficiently long to permit a prolonged study to be made, and she was again given vitamin D. No decisive changes were found during the first ten days of treatment. Roentgenograms made early during her first stay in the hospital showed slight rarefaction of the ends of the femurs, and no change in the condition of the bones took place during treatment. After treatment there was questionable rarefaction in the bones of the hands and wrists.

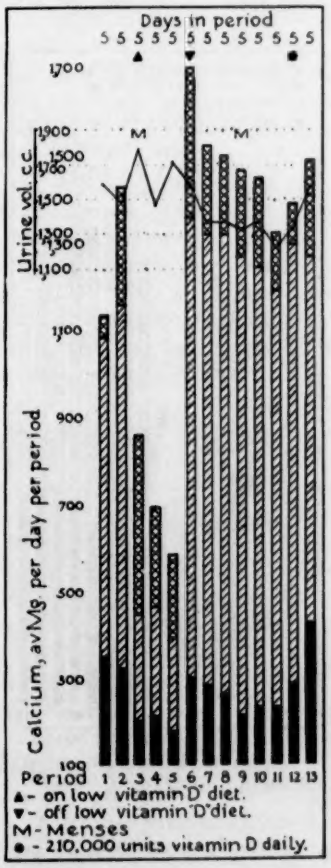

Chart 5 (case 2).—Graph showing result of second study of calcium balance beginning on March 11 and ending on May 14, 1936.

CASE 3.—F. C., a woman aged 29, has had generalized scleroderma for nine years, with marked sclerodactyly. After nine months of treatment, during which she received 240,000 U. S. P. units of vitamin D daily, she showed marked improvemetnt. There was a considerable amount of residual induration, especially of the hands. She was, however, able to clench them partially for the first time since the onset of her illness. Her hands were somewhat warmer than before

she was treated but still became cyanotic in the cold. There was approximately 50 per cent improvement except in the hands, in which improvement was about 25 per cent. There were no areas of rarefaction in bone before or during the treatment.

Case 4.—E. S., a woman aged 29, had stiffness of the hands for fifteen years, and the condition had spread gradually to the face, neck and hands. Administration of 200,000 U. S. P. units of vitamin D was begun nine months ago and is continued at the time of writing. Recently the patient gave birth to a normal, healthy child. The induration of the face and neck was distinctly improved after four months, while the hands showed little change either in the degree of induration or in the cyanosis when cold. At present the areas on the face and neck

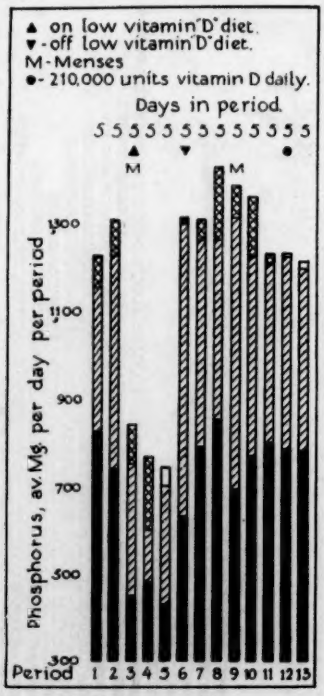
▲ on low vitamin D diet.
▼ - off low vitamin D diet.
M - Menses
● - 210,000 units vitamin D daily.
Days in period.
5 5 5 5 5 5 5 5 5 5 5 5 5 5
M
M
Phosphorus, av. Mg. per day per period
1300
1100
900
700
500
300
Period 1 2 3 4 5 6 7 8 9 10 11 12 13

Chart 6 (case 2).—Graph showing result of second study of phosphorus balance beginning on March 11 and ending on May 14, 1936.

are considerably softened. There is from 60 to 70 per cent improvement, most of the pigment remaining. The hands show less improvement but are sufficiently soft to permit clenching. They are warmer than formerly and free from pain; the degree of improvement in the hands is approximately 30 per cent.

Case 5.—M. M., a woman aged 24, first noticed stiffness of her jaws; two years later her thighs and legs became affected. She had a masklike appearance, and induration was present, being particularly marked at the angles of the jaws and less pronounced over the lower extremities. After six months of treatment with 200,000 U. S. P. units of vitamin D daily she showed approximately 50 per cent

improvement, most of the residual induration being limited to the muscles. There was little conscious impairment of chewing motion. There were small areas of rarefaction in the bones of the hands and wrists.

CASE 6.—K. L. C., a girl aged 17, had an area of morphea the size of a dollar, in the right lumbar area; the lesion had been present for two years. There was definite improvement after six months of treatment with 200,000 U. S. P. units of vitamin D daily. The brownish pigmentation of the patch and the barely visible lilac ring remained unaffected.

CASE 7.—P. T., a woman aged 39, had two areas of morphea, 1 inch and 1½ inches (2.5 and 3.8 cm.) in diameter, respectively, for five years. There was no appreciable change after she had taken 200,000 U. S. P. units of vitamin D daily for two months.

CASE 8.—J. B. S., a man aged 46, has had scleroderma for twelve years. His face and neck and parts of his trunk, wrists, hands and thighs were involved, atrophy being present in several of these areas. There was some rarefaction of the bones of the hands and wrists.

He had not improved with various treatment, including administration of thyroid and parathyroid extracts and of typhoid vaccine intravenously. He showed distinct softening of the indurated areas after seven months of treatment with 240,000 U. S. P. units of vitamin D daily, although much of the induration remained. The sharp pains in his hands had almost completely disappeared, and the sense of tightness in the chest was gone. His hands showed the least improvement, but they could be flexed farther than before treatment, and the skin was warmer and appeared less tight.

CASE 9.—C. G., a girl aged 19, first noticed stiffness of her face and neck and then of her hands about five years ago. The scleroderma improved considerably during ten months of treatment with 240,000 U. S. P. units of vitamin D daily, and her condition continues to improve at the time this report is made.

CASE 10.—A woman aged 38 has had scleroderma for twelve years. Portions of the thorax and abdomen as well as the extensor muscles of the right arm and both thighs were involved. She took 200,000 U. S. P. units of vitamin D daily for four months and 300,000 units daily for two months. There was some softening of all the affected areas, principally of those on the trunk. Considerable induration, however, still remains at the time of writing. There has been no bleaching of the pigment present over the thorax and abdomen.

CASE 11.—D. P., a woman treated at the Albert Merritt Billings Memorial Hospital by Dr. Samuel Becker and Dr. M. E. Obermayer, showed masklike stiffening of the face, morphea-like areas on the thorax and marked sclerodactyly. She was given 200,000 U. S. P. units of vitamin D daily, the dose being increased later to 240,000 units daily. After two months the morphealike parts were softer. After three months she reported she was "better in every way." No further report has been received from her.

COMMENT

The amount of a substance present in the blood may not always reflect the state of metabolism of that substance in the body. It is well known that the blood has a remarkable capacity to maintain the concentration of its constituents at a constant level, often in spite of severe pathologic conditions. Thus, for example, cholesterol may be deposited in large quantities in the skin when the blood contains normal amounts

or less. The connective tissue when in an abnormal state is particularly liable to become a depot for many metabolites. Since the blood may give only fleeting views of materials in transport, it is often necessary to examine tissues or to make balance studies in order to discover accumulations of metabolites. Thus, studies of blood chemistry alone have failed to indicate the accumulation of calcium in the soft tissues in scleroderma, while careful balance studies on two patients have shown definite retention. Presumably this retention is due to deposition of calcium in skin and muscle. The cause of this abnormal deposition is not known. All that can definitely be said is that the normal calcium metabolism is profoundly altered.

The rôle of the kidney in the entire process is not entirely clear. The calcium content of the urine of patients with scleroderma is low. Shortly after administration of large doses of vitamin D was begun in the two cases in which balance studies are reported here, the amount of calcium in the urine increased greatly, while that of the feces remained relatively unchanged. This is the characteristic effect of massive doses of vitamin D. The low calcium content of the urine helps to account for the retention of the element, and the increase in the output is sufficient to explain the negative balance observed during treatment.

It is emphasized that this is merely a symptomatic treatment, for there is no evidence that scleroderma is a deficiency disease. Further, the doses of vitamin D used are far above those required for normal growth or calcification or for recovery from rickets. From the results, both clinical and chemical, in cases in which balance studies were made and from the clinical results in the nine other cases reported here, it seems fair to say that the abnormal calcium deposits in the skin were reduced by the vitamin D therapy before any appreciable amount of calcium was removed from the bones.

The mode of action of the vitamin under these circumstances is not known. There is some evidence [15] that vitamin D acts locally on the tissue cells of the body, but further study on this point is necessary. Shelling [16] has discussed the question of the action of vitamin D on the parathyroid glands and has concluded that the evidence is against the view that the activity of vitamin D is dependent on the integrity of the parathyroid glands and in favor of the existence of an antagonism between the two. It is our belief that hyperparathyroidism does not account for all of the observations in scleroderma. We believe that the cause of scleroderma is still unknown.

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15. Gelfan, S.: Am. J. Physiol. **113**:464, 1935.

16. Shelling, David H.: The Parathyroids in Health and Disease, St. Louis, C. V. Mosby Company, 1935.

SUMMARY

A partial review of the literature on calcium metabolism in scleroderma is presented.

The view that scleroderma is a result of hyperparathyroidism is discussed.

The results of studies of calcium and phosphorus balance on two patients with scleroderma are presented, and the influence of massive doses of vitamin D on these balances is shown.

Both calcium and phosphorus are retained in the body in scleroderma. This retention can be accounted for, for the most part, by the abnormally small quantities excreted in the urine. Large doses of viosterol markedly increase the calcium content of the urine and thereby produce a loss of calcium and phosphorus from the body.

Clinical protocols of nine other patients with scleroderma are presented.

It was found that doses of from 200,000 to 300,000 international units of vitamin D daily were of benefit in scleroderma. At least four months of continuous treatment is required for improvement. Sclerodactylia improves more slowly than general scleroderma.

This treatment is not proposed for general use without further study. None of our patients has been completely cured clinically in fourteen months.

A hypothesis is offered, namely, that scleroderma is initially due to a toxin which injures the collagen syncytium and that these injured tissues secondarily take up calcium. This deposition of calcium may account for the frequently observed positive balance in scleroderma. Massive doses of vitamin D produce a negative balance, apparently at the expense of the calcium deposited in the collagen and muscle.

Dr. C. I. Reed, of the University of Illinois, gave suggestions, helped in the study and read the manuscript.

EDITORIAL

It is with a full realization of the responsibility and with deep appreciation of the honor conferred on me that I have accepted the editorship of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. It is an honor to be appointed as successor to Dr. William Allen Pusey, who has served with such distinction as editor. It would be a pleasant duty to dilate on the great distinction which Dr. Pusey has attained as a dermatologist and public-spirited citizen and to add a few words about his honesty, courage and delightful personality. This would be repeating what all the readers know. The present issue of the ARCHIVES is a tribute to a remarkable man who thoroughly deserves it.

It is hardly necessary to call attention to the high standing of the ARCHIVES and to the regard with which it is held not only in America but in foreign countries. The important part played by the American Medical Association in the publication of that journal is generally appreciated. One should not forget the able efforts of the editors of journals which preceded the ARCHIVES and whose work was carried on at times under great difficulties.

While I appreciate the difficulty of following a leader like Dr. Pusey, I can say at least that my utmost efforts will be made to maintain the ARCHIVES at its present high standard.

HOWARD FOX, M.D.